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(54) **3-ALKYL BICYCLIC [4,5,0] HYDROXAMIC ACIDS AS HDAC INHIBITORS**

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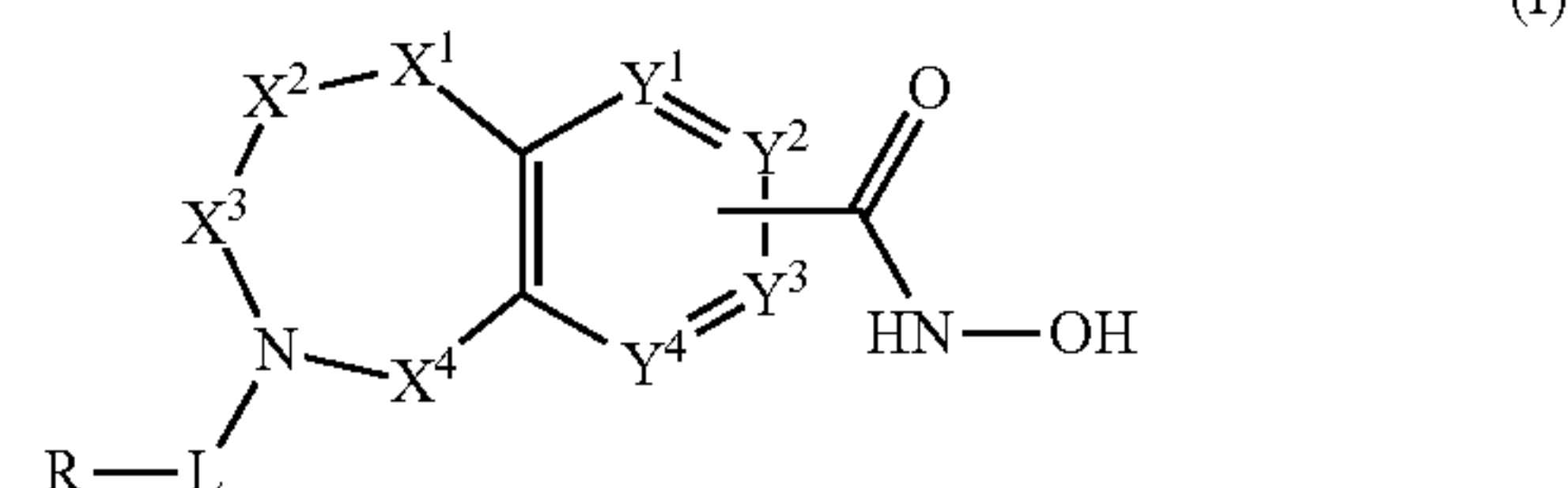
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(57) **ABSTRACT**

The present disclosure relates to inhibitors of zinc-dependent histone deacetylases (HDACs) useful in the treatment of diseases or disorders associated with an HDAC, e.g., HDAC6, having a Formula I:



where R, L, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are described herein.

**20 Claims, No Drawings**



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### 3-ALKYL BICYCLIC [4,5,0] HYDROXAMIC ACIDS AS HDAC INHIBITORS

#### CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a division of U.S. Non-Provisional Application No. 15/013,820, filed Feb. 2, 2016, which claims the benefit of priority of U.S. Provisional Application No. 62/110,716, filed Feb. 2, 2015 and U.S. Provisional Application No. 62/205,438, filed Aug. 14, 2015, each of which is incorporated herein by reference.

#### FIELD OF THE INVENTION

The present disclosure relates to inhibitors of zinc-dependent histone deacetylases (HDACs) useful in the treatment of diseases or disorders associated with HDACs including cell proliferation diseases (e.g., cancer), neurological and inflammatory diseases. Specifically, this disclosure is concerned with compounds and compositions inhibiting HDACs, methods of treating diseases associated with HDACs, and methods of synthesizing these compounds.

#### BACKGROUND OF THE INVENTION

Many members of the HDAC family require zinc (Zn) to function properly. For instance, the isozyme histone deacetylase 6 (HDAC6) is a zinc-dependent histone deacetylase that possesses histone deacetylase activity. Other family members include HDACs 1-5 and 7-11. (De Ruijter et al, *Biochem. J.* 2003, 370: 737-749).

HDAC6 is known to deacetylate and associate with  $\alpha$ -tubulin, cortactin, heat shock protein 90,  $\beta$ -catenin, glucose-regulated protein 78 kDa, myosin heavy chain 9, heat shock cognate protein 70, and dnaJ homolog subfamily A member 1 (reviewed in Li et al, *FEBS J.* 2013, 280: 775-93; Zhang et al, *Protein Cell.* 2015, 6(1): 42-54). Diseases in which HDAC6 inhibition could have a potential benefit include cancer (reviewed in Aldana-Masangkay et al, *J. Biomed. Biotechnol.* 2011, 875824), specifically: multiple myeloma (Hideshima et al, *Proc. Natl. Acad. Sci. USA* 2005, 102(24):8567-8572); lung cancer (Kamemura et al, *Biochem. Biophys. Res. Commun.* 2008, 374(1):84-89); ovarian cancer (Bazzaro et al, *Clin. Cancer Res.* 2008, 14(22):7340-7347); breast cancer (Lee et al, *Cancer Res.* 2008, 68(18): 7561-7569; Park et al, *Oncol. Rep.* 2011, 25: 1677-81; Rey et al, *Eur. J Cell Biol.* 2011, 90: 128-35); prostate cancer (Seidel et al, *Biochem. Pharmacol.* 2015 (15)00714-5); pancreatic cancer (Nawrocki et al, *Cancer Res.* 2006, 66(7): 3773-3781); renal cancer (Cha et al, *Clin. Cancer Res.* 2009, 15(3): 840-850); hepatocellular cancer (Ding et al, *FEBS Lett.* 2013, 587:880-6; Kanno et al, *Oncol. Rep.* 2012, 28: 867-73); lymphomas (Ding et al, *Cancer Cell Int.* 2014, 14:139; Amengual et al, *Clin Cancer Res.* 2015, 21(20): 4663-75); and leukemias such as acute myeloid leukemia (AML) (Fiskus et al, *Blood* 2008, 112(7):2896-2905) and acute lymphoblastic leukemia (ALL) (Rodriguez-Gonzalez et al, *Blood* 2008, 112(11): Abstract 1923)).

Inhibition of HDAC6 may also have a role in cardiovascular disease, including pressure overload, chronic ischemia, and infarction-reperfusion injury (Tannous et al, *Circulation* 2008, 117(24):3070-3078); bacterial infection, including those caused by uropathogenic *Escherichia coli* (Dhakal and Mulve, *J. Biol. Chem.* 2008, 284(1):446-454); neurological diseases caused by accumulation of intracellular protein aggregates such as Alzheimer's, Parkinson's and Hunting-

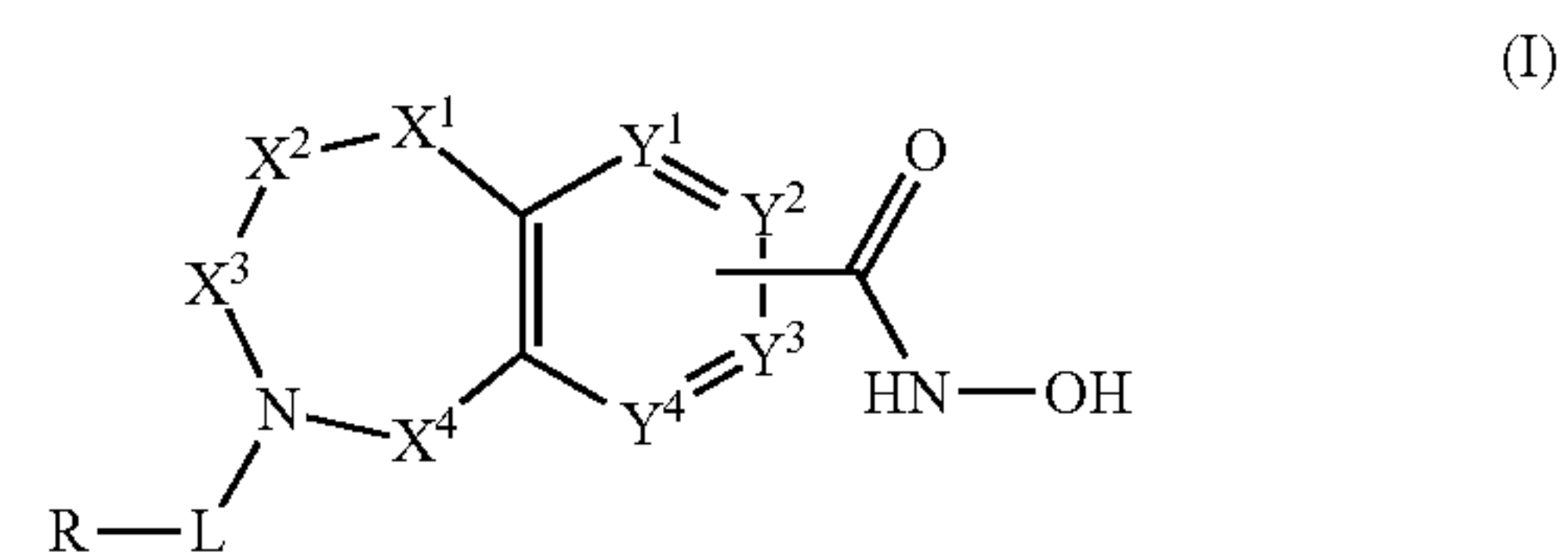
ton's disease (reviewed in Simoes-Pires et al, *Mol. Neurodegener.* 2013, 8: 7) or central nervous system trauma caused by tissue injury, oxidative-stress induced neuronal or axonal degeneration (Rivieccio et al, *Proc. Natl. Acad. Sci. USA* 2009, 106(46):19599-195604); and inflammation and autoimmune diseases through enhanced T cell-mediated immune tolerance at least in part through effects on regulatory T cells, including rheumatoid arthritis, psoriasis, spondylitis arthritis, psoriatic arthritis, multiple sclerosis, lupus, colitis and graft versus host disease (reviewed in Wang et al, *Nat. Rev. Drug Disc.* 2009 8(12):969-981; Vishwakarma et al, *Int Immunopharmacol.* 2013, 16:72-8; Kalin et al, *J. Med. Chem.* 2012, 55:639-51); and fibrotic disease, including kidney fibrosis (Choi et al, *Vascul. Pharmacol.* 2015 72:130-140).

Four HDAC inhibitors are currently approved for the treatment of some cancers. These are suberanilohydroxamic acid (Vorinostat; Zolinza®) for the treatment of cutaneous T cell lymphoma and multiple myeloma; Romidepsin (FK228; FR901228; Istodax®) for the treatment of peripheral T cell lymphoma; Panobinostat (LBH-589; Farydak®) for the treatment of multiple myeloma; and belinostat (PXD101; Beleodaq®) for the treatment of peripheral T cell lymphoma. However, these drugs are of limited effectiveness and can give rise to unwanted side effects. Thus there is a need for drugs with an improved safety-efficacy profile.

Given the complex function of HDAC6 and their potential utility in the treatment of proliferative diseases, neurological diseases, and inflammatory diseases, there is a need for HDAC inhibitors (e.g., HDAC6 inhibitors) with good therapeutic properties.

#### SUMMARY OF THE INVENTION

One aspect of the disclosure relates to compounds of Formula I:



and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers and isomers thereof, wherein:

X<sup>1</sup> is independently CR<sup>1</sup>R<sup>2</sup>, NR<sup>3</sup>, O, or C=O;

X<sup>2</sup> and X<sup>4</sup> are each independently CR<sup>1</sup>R<sup>2</sup>, C=O, S(O) or SO<sub>2</sub>;

X<sup>3</sup> is CR<sup>1</sup>R<sup>2</sup>; wherein X<sup>4</sup>, X<sup>2</sup>, and X<sup>1</sup> are not all simultaneously CR<sup>1</sup>R<sup>2</sup>;

Y<sup>1</sup> and Y<sup>4</sup> are not bonded to —C(O)NHOH and are each independently N or CR<sup>1</sup>;

Y<sup>2</sup> and Y<sup>3</sup> are each independently N or CR<sup>1</sup> when not bonded to —C(O)NHOH and Y<sup>2</sup> and Y<sup>3</sup> are C when bonded to —C(O)NHOH;

L is a bond, —(CR<sup>1</sup>R<sup>2</sup>)<sub>n</sub>—, —C(O)O—, —C(O)NR<sup>3</sup>—, —S(O)<sub>2</sub>—, —S(O)<sub>2</sub>NR<sup>3</sup>—, —S(O)—, or —S(O)NR<sup>3</sup>—, wherein L is bound to the ring nitrogen through the carbonyl or sulfonyl group;

R is independently —H, —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>2</sub>-C<sub>6</sub> alkenyl, —C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, —C<sub>2</sub>-C<sub>6</sub> alkynyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, —C<sub>5</sub>-C<sub>12</sub> spirocycle, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, wherein



## 3

each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, spirocycle, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl is optionally substituted with one or more —OH, halogen, oxo, —NO<sub>2</sub>, —CN, —R<sup>1</sup>, —R<sup>2</sup>, —OR<sup>3</sup>, —NHR<sup>3</sup>, —NR<sup>3</sup>R<sup>4</sup>, —S(O)<sub>2</sub>NR<sup>3</sup>R<sup>4</sup>, —S(O)<sub>2</sub>R<sup>1</sup>, —C(O)R<sup>1</sup>, or —CO<sub>2</sub>R<sup>1</sup>, —NR<sup>3</sup>S(O)<sub>2</sub>R<sup>1</sup>, —S(O)R<sup>1</sup>, —S(O)NR<sup>3</sup>R<sup>4</sup>, —NR<sup>3</sup>S(O)R<sup>1</sup>, heterocycle, aryl, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O;

each R<sup>1</sup> and R<sup>2</sup> are independently, and at each occurrence, —H, —R<sup>3</sup>, —R<sup>4</sup>, —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>2</sub>-C<sub>6</sub> alkenyl, —C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, —C<sub>2</sub>-C<sub>6</sub> alkynyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, —OH, halogen, —NO<sub>2</sub>, —CN, —NHC<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>R<sup>5</sup>, —S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), —(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>R<sup>5</sup>, —C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, —CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, or —(CHR<sup>5</sup>)<sub>n</sub>NR<sup>3</sup>R<sup>4</sup>, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from —OH, halogen, —NO<sub>2</sub>, oxo, —CN, —R<sup>5</sup>, —OR<sup>3</sup>, —NHR<sup>3</sup>, NR<sup>3</sup>R<sup>4</sup>, —S(O)<sub>2</sub>N(R<sup>3</sup>)<sub>2</sub>, —S(O)<sub>2</sub>R<sup>5</sup>, —C(O)R<sup>5</sup>, —CO<sub>2</sub>R<sup>5</sup>, —NR<sup>3</sup>S(O)<sub>2</sub>R<sup>5</sup>, —S(O)R<sup>5</sup>, —S(O)NR<sup>3</sup>R<sup>4</sup>, —NR<sup>3</sup>S(O)R<sup>5</sup>, heterocycle, aryl, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O;

or R<sup>1</sup> and R<sup>2</sup> can combine with the carbon atom to which they are both attached to form a spirocycle, spiroheterocycle, or a spirocycloalkenyl;

or R<sup>1</sup> and R<sup>2</sup>, when on adjacent atoms, can combine to form a heterocycle, cycloalkyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or cycloalkenyl;

or R<sup>1</sup> and R<sup>2</sup>, when on non-adjacent atoms, can combine to form a bridging cycloalkyl or heterocycloalkyl;

R<sup>1'</sup> and R<sup>2'</sup> are independently, and at each occurrence, —H, —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>2</sub>-C<sub>6</sub> alkenyl, —C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, —C<sub>2</sub>-C<sub>6</sub> alkynyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocyclyl, —OH, halogen, —NO<sub>2</sub>, —CN, —NHC<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>R<sup>5</sup>, —S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), —(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>R<sup>5</sup>, —C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, —CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, or (CHR<sup>5</sup>)<sub>n</sub>NR<sup>3</sup>R<sup>4</sup>, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, or heterocyclyl is optionally substituted with one or more substituents selected from —OH, halogen, —NO<sub>2</sub>, oxo, —CN, —R<sup>5</sup>, —OR<sup>3</sup>, —NHR<sup>3</sup>, NR<sup>3</sup>R<sup>4</sup>, —S(O)<sub>2</sub>N(R<sup>3</sup>)<sub>2</sub>, —S(O)<sub>2</sub>R<sup>5</sup>, —C(O)R<sup>5</sup>, —CO<sub>2</sub>R<sup>5</sup>, —NR<sup>3</sup>S(O)<sub>2</sub>R<sup>5</sup>, —S(O)R<sup>5</sup>, —S(O)NR<sup>3</sup>R<sup>4</sup>, —NR<sup>3</sup>S(O)R<sup>5</sup>, heterocycle, aryl, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O;

or R<sup>1'</sup> and R<sup>2'</sup> can combine with the carbon atom to which they are both attached to form a spirocycle, spiroheterocycle, or a spirocycloalkenyl;

or R<sup>1'</sup> and R<sup>2'</sup> can combine with R<sup>1</sup> or R<sup>2</sup> on adjacent atoms to form a heterocycle, cycloalkyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or cycloalkenyl;

or R<sup>1'</sup> and R<sup>2'</sup> can combine with R<sup>1</sup> or R<sup>2</sup> on non-adjacent atoms, to form a bridging cycloalkyl or heterocycloalkyl;

R<sup>3</sup> and R<sup>4</sup> are independently, at each occurrence, —H, —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>2</sub>-C<sub>6</sub> alkenyl, —C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, —C<sub>2</sub>-C<sub>6</sub> alkynyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, —S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), —(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>R<sup>5</sup>, —C(O)C<sub>1</sub>-

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C<sub>6</sub> alkyl, —CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, or —(CHR<sup>5</sup>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more substituents selected from —OH, halogen, —NO<sub>2</sub>, Oxo, —CN, —R<sup>5</sup>, —O(C<sub>1</sub>-C<sub>6</sub> alkyl), —NH(C<sub>1</sub>-C<sub>6</sub> alkyl), —N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), —C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, —CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —S(O)R<sup>5</sup>, —S(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)R<sup>5</sup>, heterocycle, aryl, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O;

or R<sup>3</sup> and R can combine with the nitrogen atom to which they are attached to form a heterocycle, wherein each heterocycle or heteroaryl is optionally substituted by —R<sup>1</sup>, —R<sup>2</sup>, —R<sup>4</sup>, —OR<sup>4</sup>, or —NR<sup>4</sup>R<sup>5</sup>;

R<sup>5</sup> is independently, and at each occurrence, —H, —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>2</sub>-C<sub>6</sub> alkenyl, —C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, —C<sub>2</sub>-C<sub>6</sub> alkynyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, —OH, halogen, —NO<sub>2</sub>, —CN, —NHC<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), —S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, —CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —S(O)(C<sub>1</sub>-C<sub>6</sub> alkyl), —S(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)(C<sub>1</sub>-C<sub>6</sub> alkyl) or —(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>; and

n is independently, and at each occurrence, an integer from 0 to 6 and;

provided that when X<sup>2</sup> and X<sup>4</sup> are both C=O, X<sup>1</sup> is not NR<sup>3</sup>.

Another aspect of the disclosure relates to a method of treating a disease or disorder associated with HDAC, e.g., HDAC6 modulation in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula I.

Another aspect of the disclosure is directed to a method of inhibiting an HDAC, e.g., HDAC6. The method involves administering to a patient in need thereof an effective amount of a compound of Formula I.

Another aspect of the disclosure relates to a compound of Formula I, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, for use in treating or preventing a disease associated with HDAC6 modulation.

Another aspect of the disclosure relates to the use of a compound of Formula I, or a pharmaceutically acceptable salt, prodrug, solvate, hydrate, tautomer, or isomer thereof, in the manufacture of a medicament for treating or preventing a disease associated with HDAC6 modulation.

Another aspect of the disclosure is directed to pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier can further include an excipient, diluent, or surfactant. The pharmaceutical composition can be effective for treating a disease or disorder associated with HDAC, e.g., HDAC6, modulation in a subject in need thereof. The pharmaceutical compositions can comprise the compounds of the present disclosure for use in treating diseases described herein. The compositions can contain at least one compound of the disclosure and a pharmaceutically acceptable carrier. The disclosure also provides the use of the compounds described herein in the manufacture of a medicament for the treatment of a disease associated with HDACs.

The present disclosure also provides methods for the treatment of human diseases or disorders including, without



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limitation, oncological, neurological, inflammatory, autoimmune, infectious, metabolic, hematologic, or cardiovascular diseases or disorders.

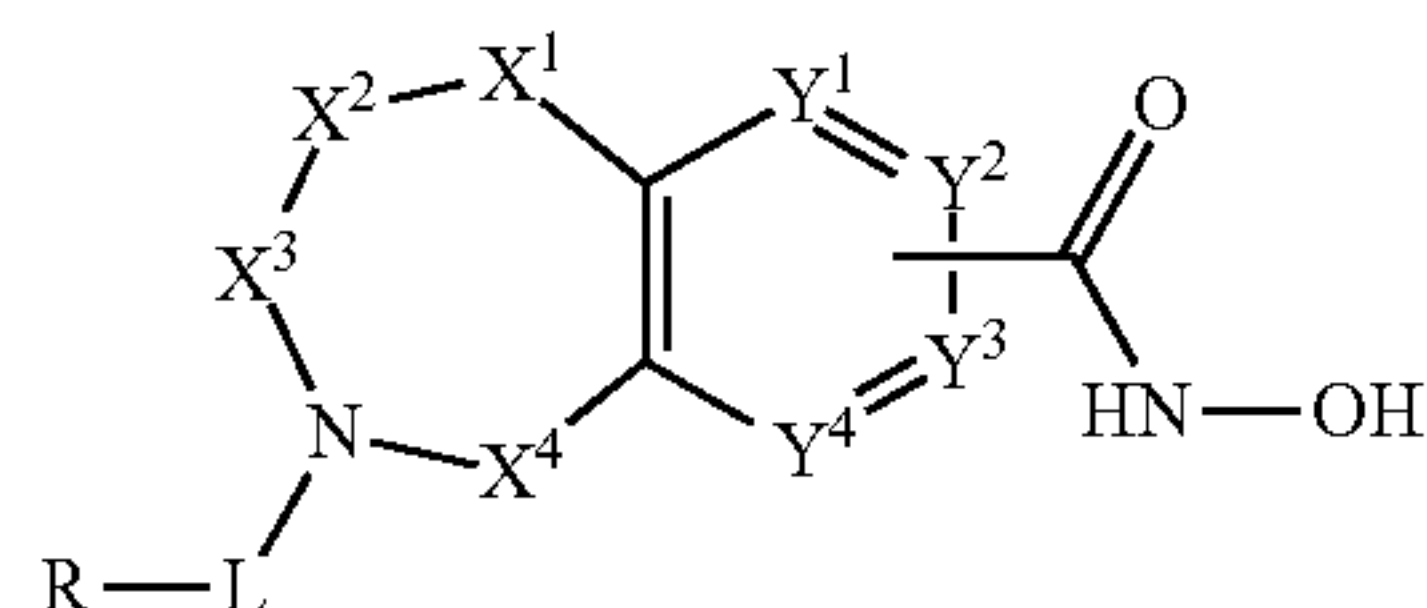
The present disclosure also provides compounds that are useful in inhibiting of zinc-dependent HDAC enzymes, for instance HDAC6. These compounds can also be useful in the treatment of diseases including cancer.

The present disclosure further provides compounds that can inhibit an HDAC, e.g., HDAC6. In some embodiments, the efficacy-safety profile of the compounds of the current disclosure can be improved relative to other known HDAC (e.g. HDAC6) inhibitors. Additionally, the present technology also has the advantage of being able to be used for a number of different types of diseases, including cancer and non-cancer indications. Additional features and advantages of the present technology will be apparent to one of skill in the art upon reading the Detailed Description of the Disclosure, below.

### DETAILED DESCRIPTION OF THE INVENTION

HDAC6 is a zinc-dependent histone deacetylase that has two catalytic domains. HDAC6 can interact with and deacetylate non-histone proteins, including HSP90 and  $\alpha$ -tubulin. Acetylation of HSP90 is associated with loss of function of HSP90. HDAC6 is also implicated in the degradation of misfolded proteins as part of the aggresome. Accordingly, inhibition of HDAC6 can have downstream effects that can play a role in the development of certain diseases such as cancer. The present disclosure provides inhibitors of HDACs, e.g., HDAC6 and methods for using the same to treat disease.

In a first aspect of the disclosure, compounds of the Formula I are described:



and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof, wherein R, L, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are described as above.

The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

#### Definitions

The articles “a” and “an” are used in this disclosure to refer to one or more than one (e.g., to at least one) of the

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grammatical object of the article. By way of example, “an element” means one element or more than one element.

The term “and/or” is used in this disclosure to mean either “and” or “or” unless indicated otherwise.

The term “optionally substituted” is understood to mean that a given chemical moiety (e.g., an alkyl group) can (but is not required to) be bonded other substituents (e.g., heteroatoms). For instance, an alkyl group that is optionally substituted can be a fully saturated alkyl chain (e.g. a pure hydrocarbon). Alternatively, the same optionally substituted alkyl group can have substituents different from hydrogen. For instance, it can, at any point along the chain be bounded to a halogen atom, a hydroxyl group, or any other substituent described herein. Thus the term “optionally substituted” means that a given chemical moiety has the potential to contain other functional groups, but does not necessarily have any further functional groups.

The term “aryl” refers to cyclic, aromatic hydrocarbon groups that have 1 to 2 aromatic rings, including monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (e.g., biphenyl), or fused (e.g., naphthyl). The aryl group may be optionally substituted by one or more substituents, e.g., 1 to 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, —H, —halogen, —O—C<sub>1</sub>—C<sub>6</sub> alkyl, —C<sub>1</sub>—C<sub>6</sub> alkyl, —OC<sub>2</sub>—C<sub>6</sub> alkenyl, —OC<sub>2</sub>—C<sub>6</sub> alkynyl, —C<sub>2</sub>—C<sub>6</sub> alkenyl, —C<sub>2</sub>—C<sub>6</sub> alkynyl, —OH, —OP(O)(OH)<sub>2</sub>, —OC(O)C<sub>1</sub>—C<sub>6</sub> alkyl, —C(O)C<sub>1</sub>—C<sub>6</sub> alkyl, —OC(O)OC<sub>1</sub>—C<sub>6</sub> alkyl, —NH<sub>2</sub>, —NH(C<sub>1</sub>—C<sub>6</sub> alkyl), —N(C<sub>1</sub>—C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>—C<sub>1</sub>—C<sub>6</sub> alkyl, —S(O)NHC<sub>1</sub>—C<sub>6</sub> alkyl, and —S(O)N(C<sub>1</sub>—C<sub>6</sub> alkyl)<sub>2</sub>. The substituents can themselves be optionally substituted. Furthermore when containing two fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these aryl groups include indanyl, indenyl, tetrahydronaphthalenyl, and tetrahydrobenzoannulenyl.

Unless otherwise specifically defined, “heteroaryl” means a monovalent monocyclic aromatic radical of 5 to 24 ring atoms or a polycyclic aromatic radical, containing one or more ring heteroatoms selected from N, S, P, and O, the remaining ring atoms being C. Heteroaryl as herein defined also means a bicyclic heteroaromatic group wherein the heteroatom is selected from N, S, P, and O. The aromatic radical is optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, furyl, thienyl, pyrrolyl, pyridyl, pyrazolyl, pyrimidinyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyrazinyl, indolyl, thiophen-2-yl, quinolyl, benzopyranlyl, isothiazolyl, thiazolyl, thiadiazole, indazole, benzimidazolyl, thieno[3,2-b]thiophene, triazolyl, triazinyl, imidazo[1,2-b]pyrazolyl, furo[2,3-c]pyridinyl, imidazo[1,2-a]pyridinyl, indazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrazolo[3,4-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-c]pyridinyl, thieno[2,3-b]pyridinyl, benzothiazolyl, indolyl, indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, benzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, dihydrobenzoxanyl, quinolinyl, isoquinolinyl, 1,6-naphthyridinyl, benzo[de]isoquinolinyl, pyrido[4,3-b][1,6]naphthyridinyl, thieno[2,3-b]pyrazinyl, quinazolinyl, tetrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, isoindolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,4-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, imidazo[5,4-b]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, tetrahydro pyrrolo[1,2-a]pyrimidinyl, 3,4-dihydro-2H-1  $\lambda^2$ -pyrrolo[2,1-b]pyrimidine, dibenzo[b,d]



thiophene, pyridin-2-one, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1H-pyrido[3,4-b][1,4]thiazinyl, benzooxazolyl, benzoisoxazolyl, furo[2,3-b]pyridinyl, benzothiophenyl, 1,5-naphthyridinyl, furo[3,2-b]pyridine, [1,2,4]triazolo[1,5-a]pyridinyl, benzo[1,2,3]triazolyl, imidazo[1,2-a]pyrimidinyl, [1,2,4]triazolo[4,3-b]pyridazinyl, benzo[c][1,2,5]thiadiazolyl, benzo[c][1,2,5]oxadiazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, 3,4-dihydro-2H-pyrazolo[1,5-b][1,2]oxazinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, thiazolo[5,4-d]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, thieno[2,3-b]pyrrolyl, 3H-indolyl, and derivatives thereof. Furthermore when containing two fused rings the heteroaryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these heteroaryl groups include indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, 3,4-dihydro-1H-isoquinolinyl, 2,3-dihydrobenzofuran, indolinyl, indolyl, and dihydrobenzoxanyl.

“Alkyl” refers to a straight or branched chain saturated hydrocarbon. C<sub>1</sub>-C<sub>6</sub> alkyl groups contain 1 to 6 carbon atoms. Examples of a C<sub>1</sub>-C<sub>6</sub> alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, sec-butyl and tert-butyl, isopentyl and neopentyl.

The term “alkenyl” means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 6 carbon atoms in the chain. Alkenyl groups can have 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl, or propyl are attached to a linear alkenyl chain. Exemplary alkenyl groups include ethenyl, propenyl, n-butenyl, and i-butenyl. A C<sub>2</sub>-C<sub>6</sub> alkenyl group is an alkenyl group containing between 2 and 6 carbon atoms.

The term “alkynyl” means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 6 carbon atoms in the chain. Alkynyl groups can have 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl, or propyl are attached to a linear alkynyl chain. Exemplary alkynyl groups include ethynyl, propynyl, n-butylnyl, 2-butylnyl, 3-methylbutynyl, and n-pentylnyl. A C<sub>2</sub>-C<sub>6</sub> alkynyl group is an alkynyl group containing between 2 and 6 carbon atoms.

The term “cycloalkyl” means monocyclic or polycyclic saturated carbon rings containing 3-18 carbon atoms. Examples of cycloalkyl groups include, without limitations, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, cyclooctanyl, norboranyl, norborenyl, bicyclo[2.2.2]octanyl, or bicyclo[2.2.2]octenyl. A C<sub>3</sub>-C<sub>8</sub> cycloalkyl is a cycloalkyl group containing between 3 and 8 carbon atoms. A cycloalkyl group can be fused (e.g., decalin) or bridged (e.g., norbornane).

The term “cycloalkenyl” means monocyclic, non-aromatic unsaturated carbon rings containing 4-18 carbon atoms. Examples of cycloalkenyl groups include, without limitation, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and norborenyl. A C<sub>4</sub>-C<sub>8</sub> cycloalkenyl is a cycloalkenyl group containing between 4 and 8 carbon atoms.

The terms “heterocyclyl” or “heterocycloalkyl” or “heterocycle” refer to monocyclic or polycyclic 3 to 24-membered rings containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur and wherein there is not delocalized  $\pi$ electrons (aromaticity) shared among the ring carbon or heteroatoms. Heterocyclyl rings include, but are not limited to, oxetanyl, azetadiny, tetrahydrofuranyl, pyrro-

lidinyl, oxazoliny, oxazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxaliny, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepiny, oxepiny, diazepiny, tropanyl, and homotropanyl. A heterocyclyl or heterocycloalkyl ring can also be fused or bridged, e.g., can be a bicyclic ring.

As used herein, the term “halo” or “halogen” means fluoro, chloro, bromo, or iodo.

The term “carbonyl” refers to a functional group composing a carbon atom double-bonded to an oxygen atom. It can be abbreviated herein as “oxo”, as C(O), or as C=O.

“Spirocycle” or “spirocyclic” means carbogenic bicyclic ring systems with both rings connected through a single atom. The ring can be different in size and nature, or identical in size and nature. Examples include spiropentane, spirohexane, spiroheptane, spirooctane, spirononane, or spirodecane. One or both of the rings in a spirocycle can be fused to another ring carbocyclic, heterocyclic, aromatic, or heteroaromatic ring. One or more of the carbon atoms in the spirocycle can be substituted with a heteroatom (e.g., O, N, S, or P). A C<sub>3</sub>-C<sub>12</sub> spirocycle is a spirocycle containing between 3 and 12 carbon atoms. One or more of the carbon atoms can be substituted with a heteroatom.

The term “spirocyclic heterocycle” or “spiroheterocycle” is understood to mean a spirocycle wherein at least one of the rings is a heterocycle (e.g., at least one of the rings is furanyl, morpholinyl, or piperadiny).

The disclosure also includes pharmaceutical compositions comprising an effective amount of a disclosed compound and a pharmaceutically acceptable carrier. Representative “pharmaceutically acceptable salts” include, e.g., water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavuliate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, sethionate, lactate, lactobionate, laurate, magnesium, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

The term “stereoisomers” refers to the set of compounds which have the same number and type of atoms and share the same bond connectivity between those atoms, but differ in three dimensional structure. The term “stereoisomer” refers to any member of this set of compounds.

The term “diastereomers” refers to the set of stereoisomers which cannot be made superimposable by rotation around single bonds. For example, cis- and trans-double bonds, endo- and exo-substitution on bicyclic ring systems, and compounds containing multiple stereogenic centers with different relative configurations are considered to be diastereomers. The term “diastereomer” refers to any member of this set of compounds. In some examples presented, the synthetic route may produce a single diastereomer or a mixture of diastereomers. In some cases these diastereomers



were separated and in other cases a wavy bond is used to indicate the structural element where configuration is variable.

The term “enantiomers” refers to a pair of stereoisomers which are non-superimposable mirror images of one another. The term “enantiomer” refers to a single member of this pair of stereoisomers. The term “racemic” refers to a 1:1 mixture of a pair of enantiomers.

The term “tautomers” refers to a set of compounds that have the same number and type of atoms, but differ in bond connectivity and are in equilibrium with one another. A “tautomer” is a single member of this set of compounds. Typically a single tautomer is drawn but it is understood that this single structure is meant to represent all possible tautomers that might exist. Examples include enol-ketone tautomerism. When a ketone is drawn it is understood that both the enol and ketone forms are part of the disclosure.

An “effective amount” when used in connection with a compound is an amount effective for treating or preventing a disease in a subject as described herein.

The term “carrier”, as used in this disclosure, encompasses carriers, excipients, and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body of a subject.

The term “treating” with regard to a subject, refers to improving at least one symptom of the subject’s disorder. Treating includes curing, improving, or at least partially ameliorating the disorder.

The term “disorder” is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

The term “administer”, “administering”, or “administration” as used in this disclosure refers to either directly administering a disclosed compound or pharmaceutically acceptable salt of the disclosed compound or a composition to a subject, or administering a prodrug derivative or analog of the compound or pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject’s body.

The term “prodrug,” as used in this disclosure, means a compound which is convertible in vivo by metabolic means (e.g., by hydrolysis) to a disclosed compound. Furthermore, as used herein a prodrug is a drug which is inactive in the body, but is transformed in the body typically either during absorption or after absorption from the gastrointestinal tract into the active compound. The conversion of the prodrug into the active compound in the body may be done chemically or biologically (e.g., using an enzyme).

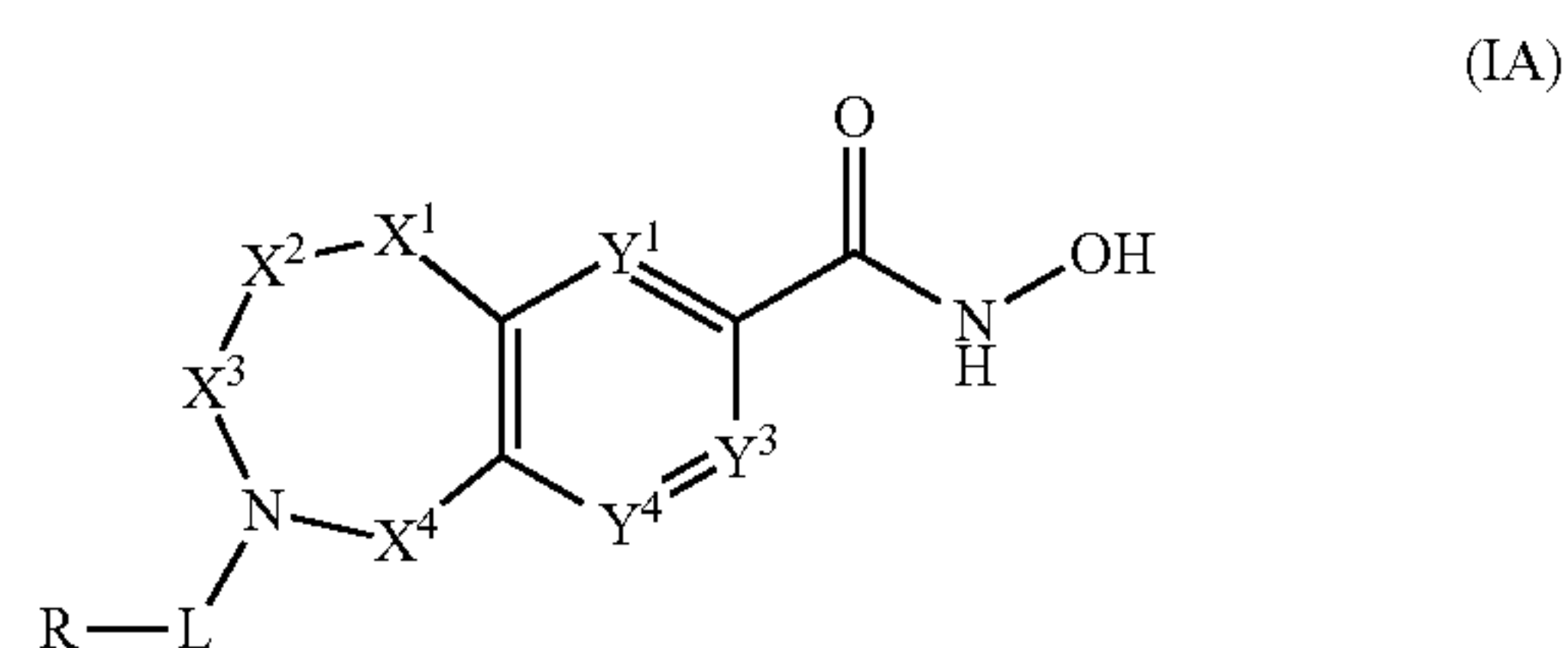
The term “solvate” refers to a complex of variable stoichiometry formed by a solute and solvent. Such solvents for the purpose of the disclosure may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, MeOH, EtOH, and AcOH. Solvates wherein water is the solvent molecule are typically referred to as hydrates. Hydrates include compositions containing stoichiometric amounts of water, as well as compositions containing variable amounts of water.

The term “isomer” refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light (stereoisomers). With regard to stereoisomers, the compounds of Formula I may

have one or more asymmetric carbon atom and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers.

A “patient” or “subject” is a mammal, e.g., a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus.

In another embodiment of the disclosure are described compounds of the Formula IA:



and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers or isomer thereof; where R, L, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, Y<sup>1</sup>, Y<sup>3</sup>, and Y<sup>4</sup> are defined as above in Formula I.

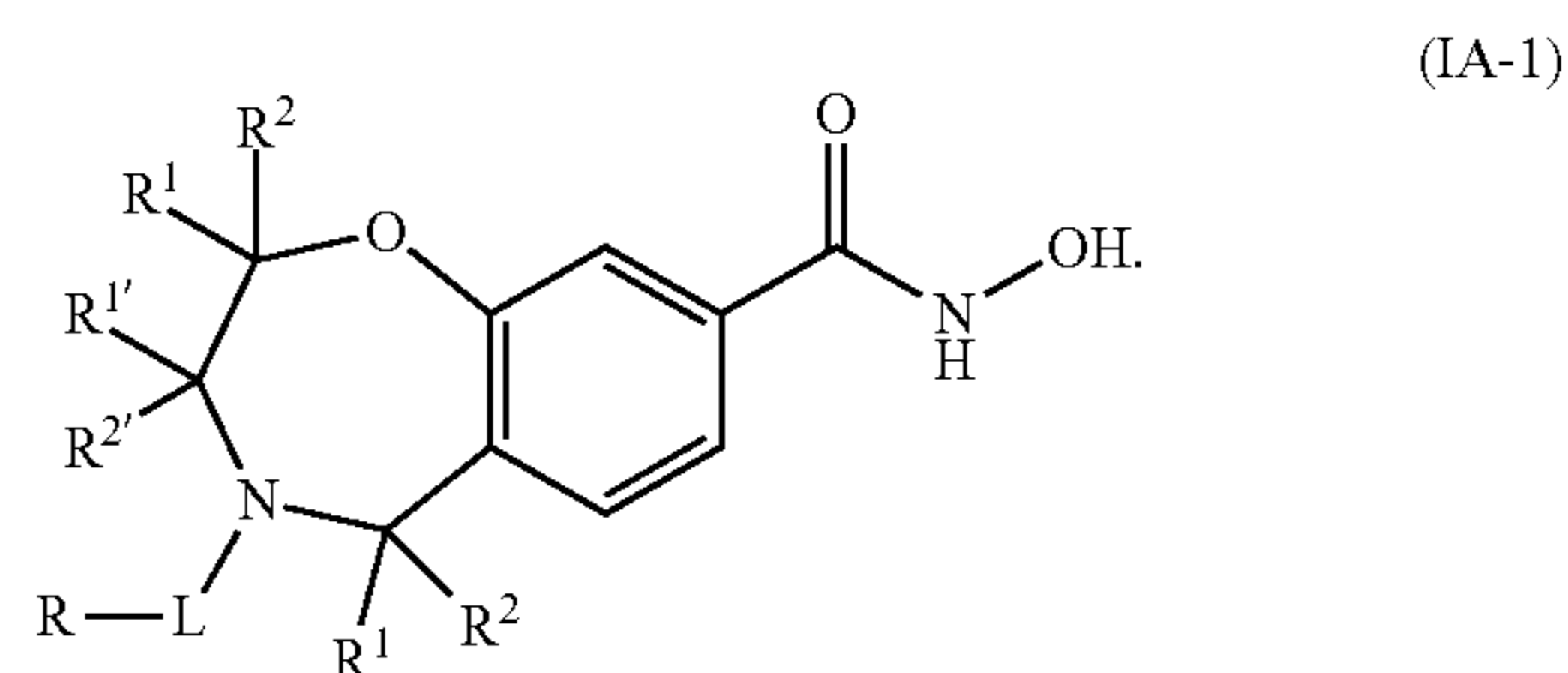
In another embodiment of the compounds of Formula IA, X<sup>4</sup> is CR<sup>1</sup>R<sup>2</sup>.

In another embodiment of the compounds of Formula IA, X<sup>1</sup> is NR<sup>3</sup>, O, or C=O.

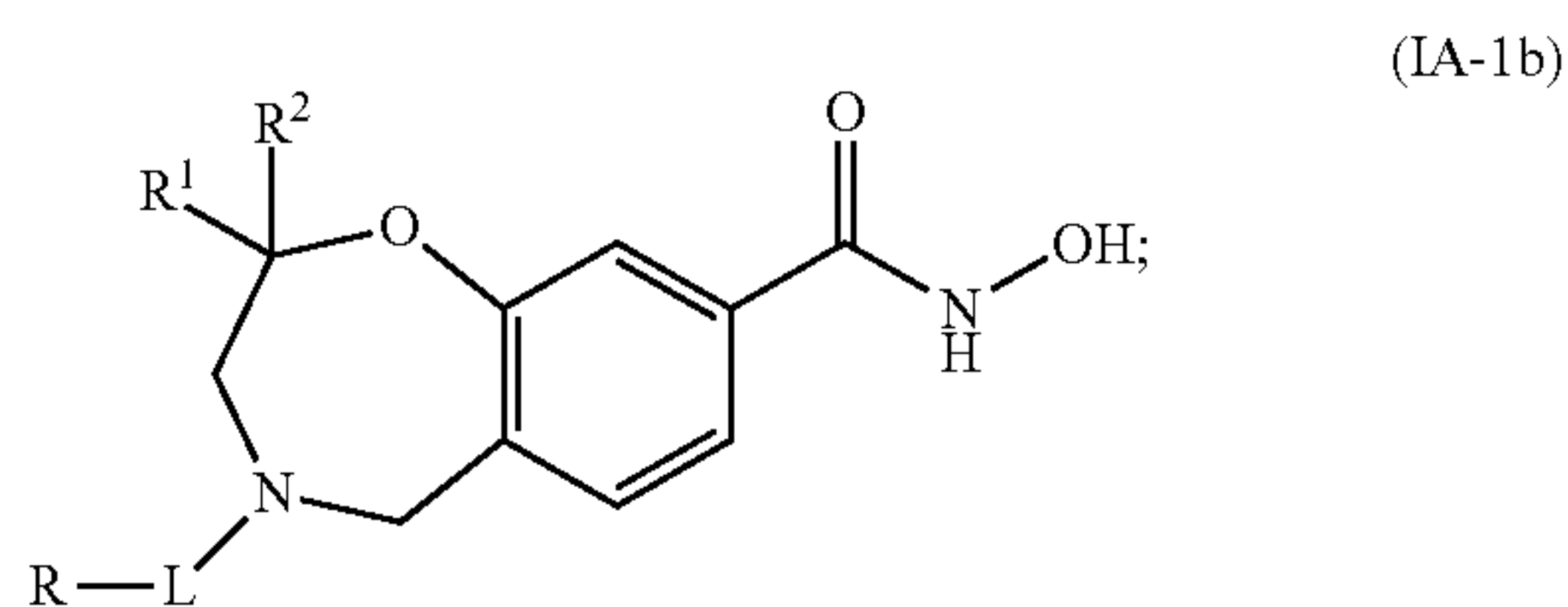
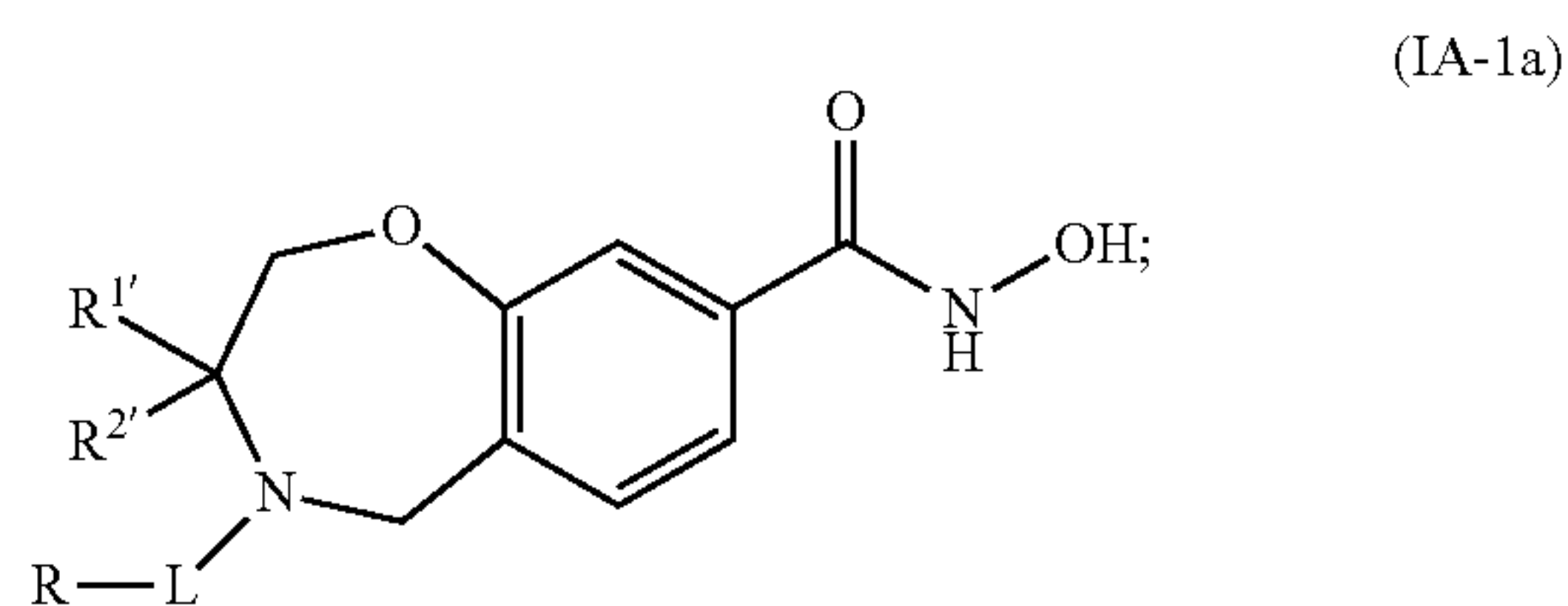
In another embodiment of the compounds of Formula IA, X<sup>1</sup> is O.

In another embodiment of the compounds of Formula IA, X<sup>1</sup> is O and X<sup>4</sup> is CR<sup>1</sup>R<sup>2</sup>.

In some embodiments of the disclosure, the compounds of Formula IA may be of the Formula IA-1:



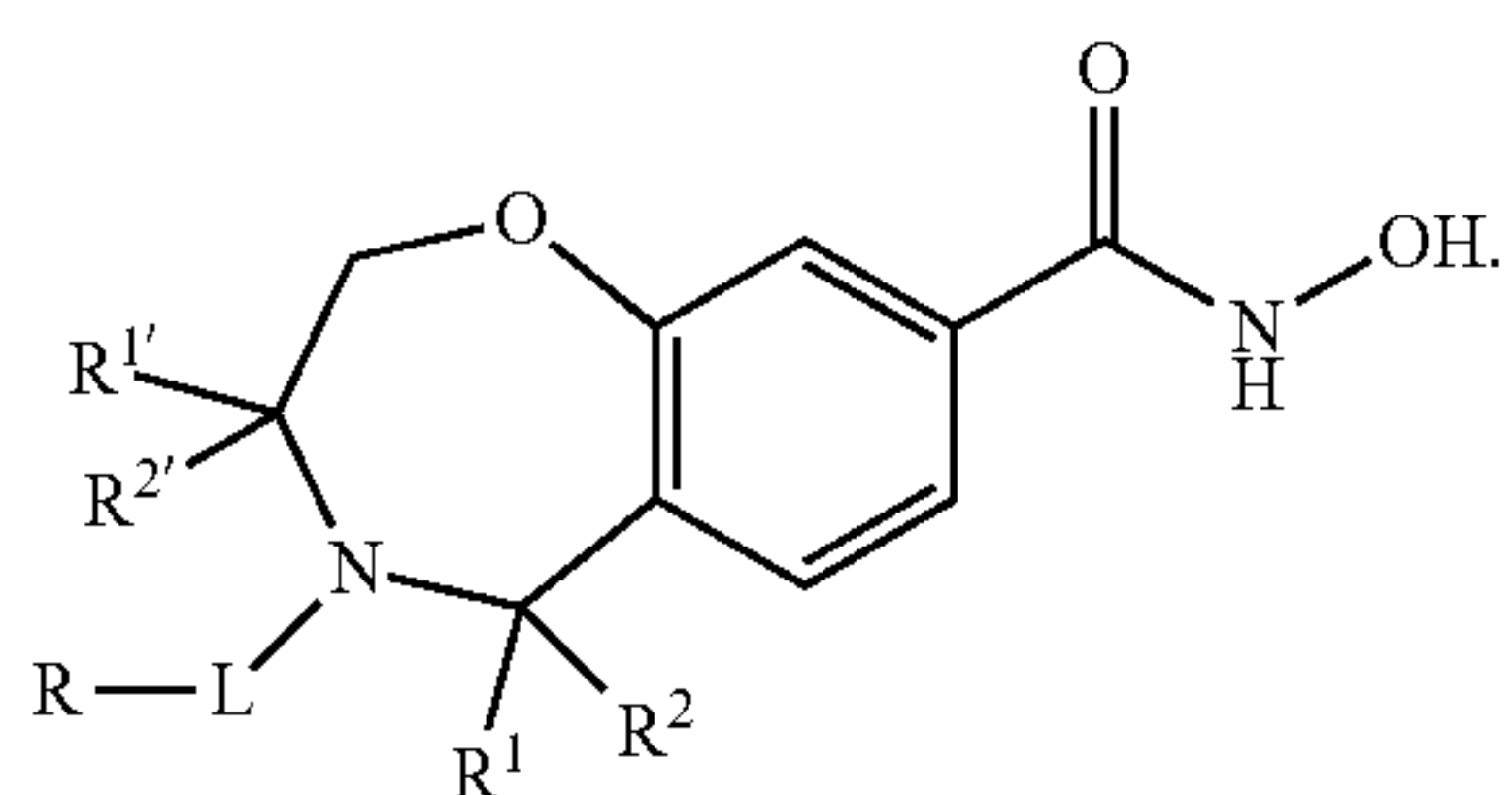
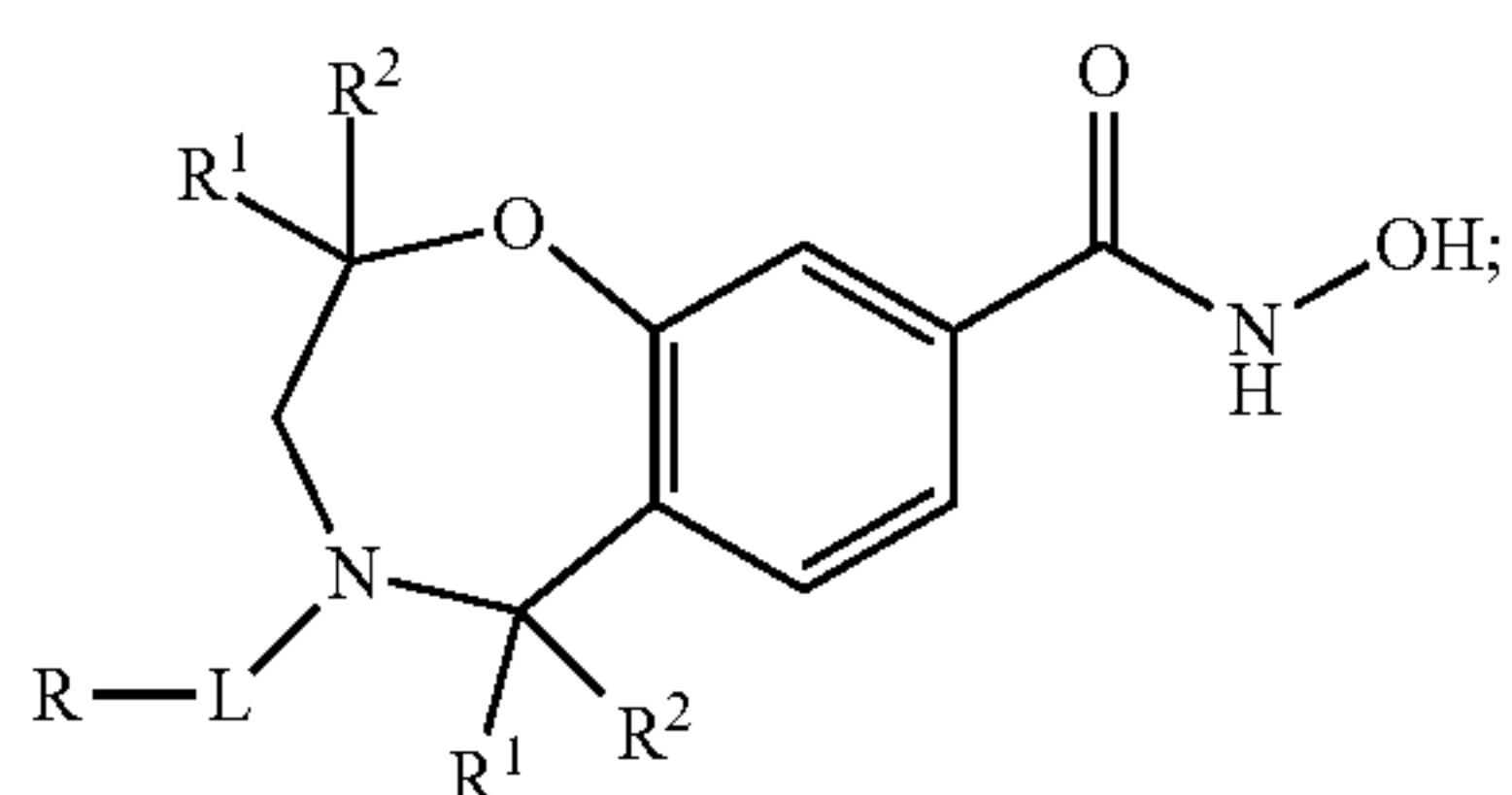
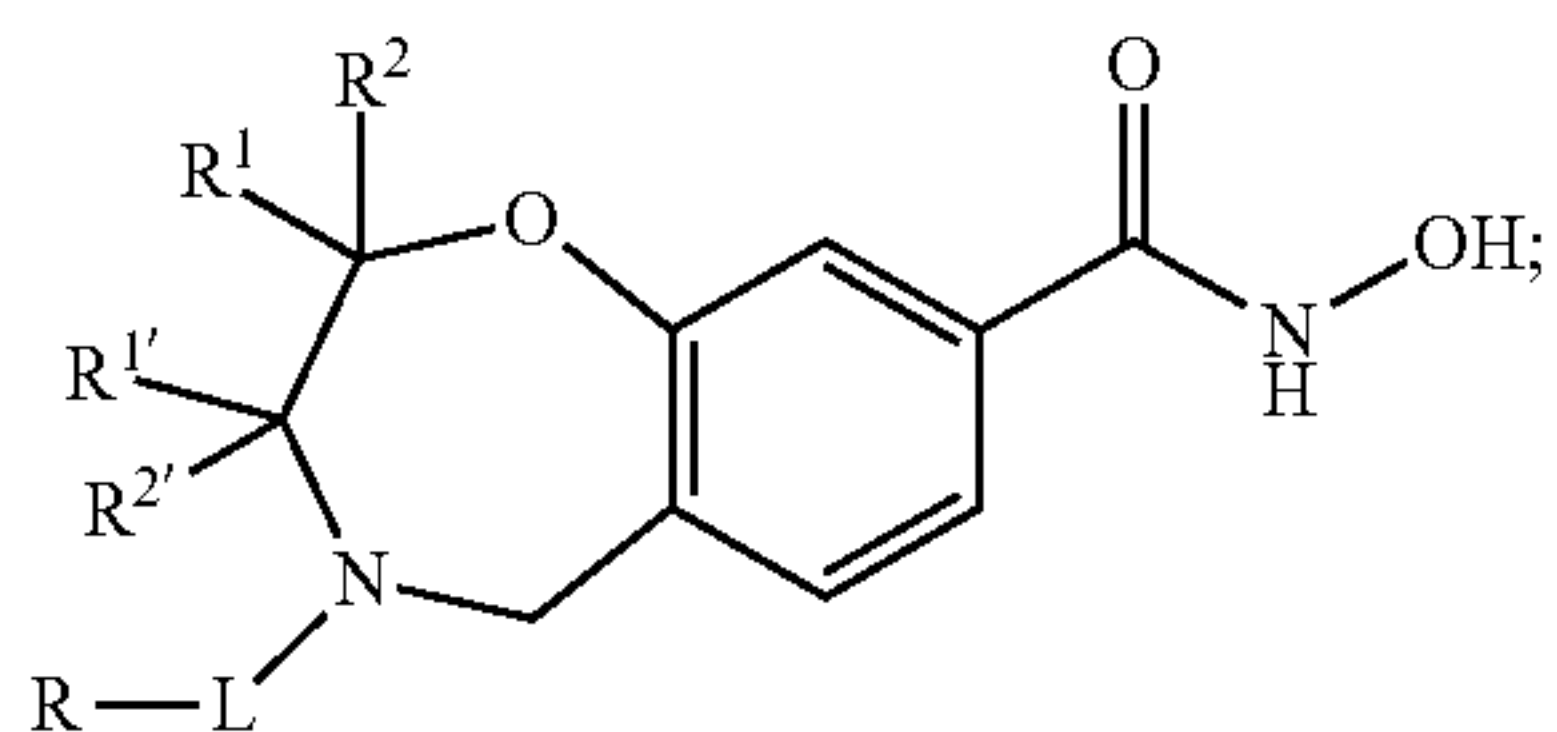
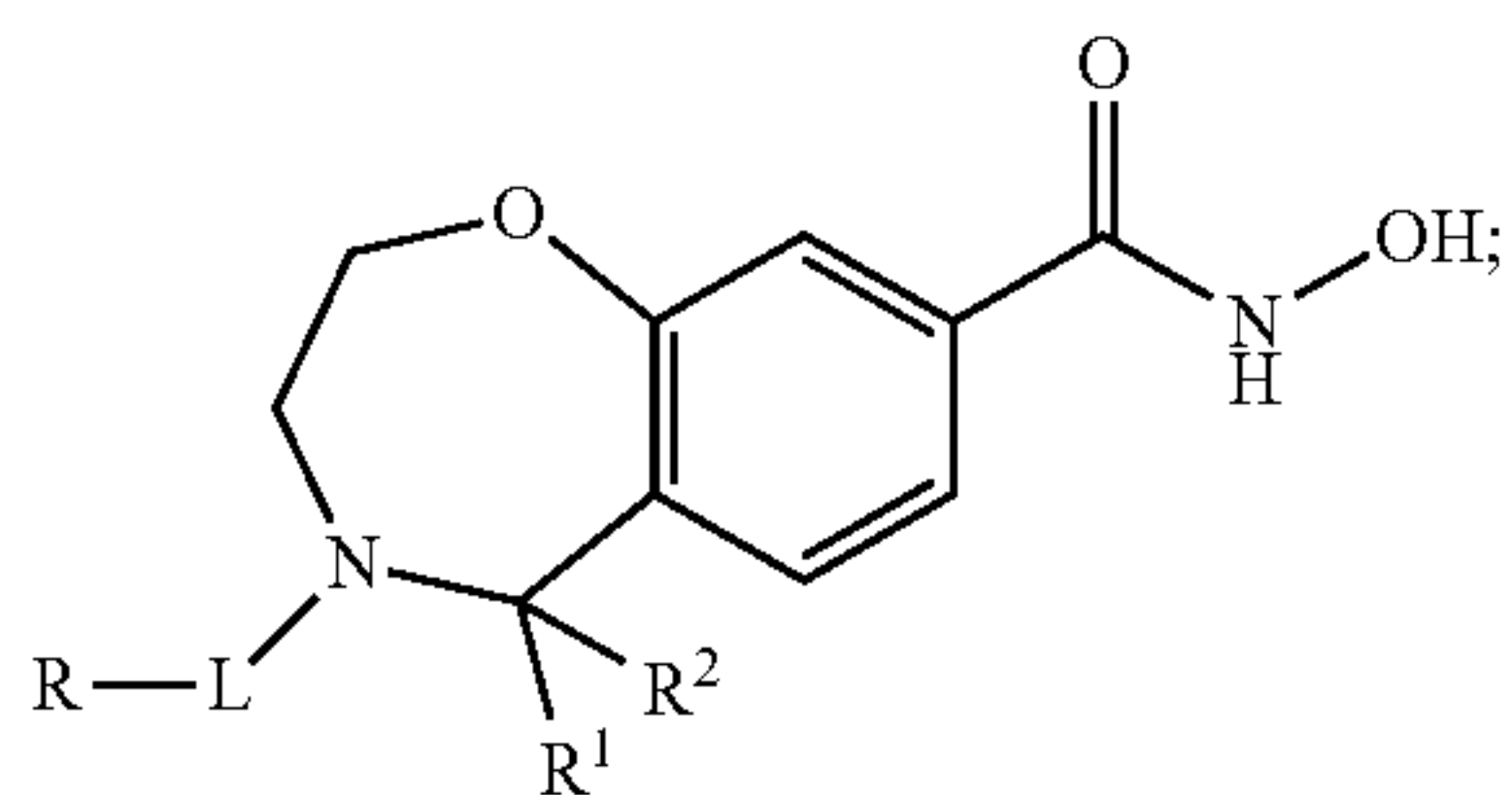
For instance, in some embodiments of Formula IA-1, the compounds can be of the Formula IA-1a, Formula IA-1b, Formula IA-1c, Formula IA-1d, Formula IA-1e, or Formula IA-1f:



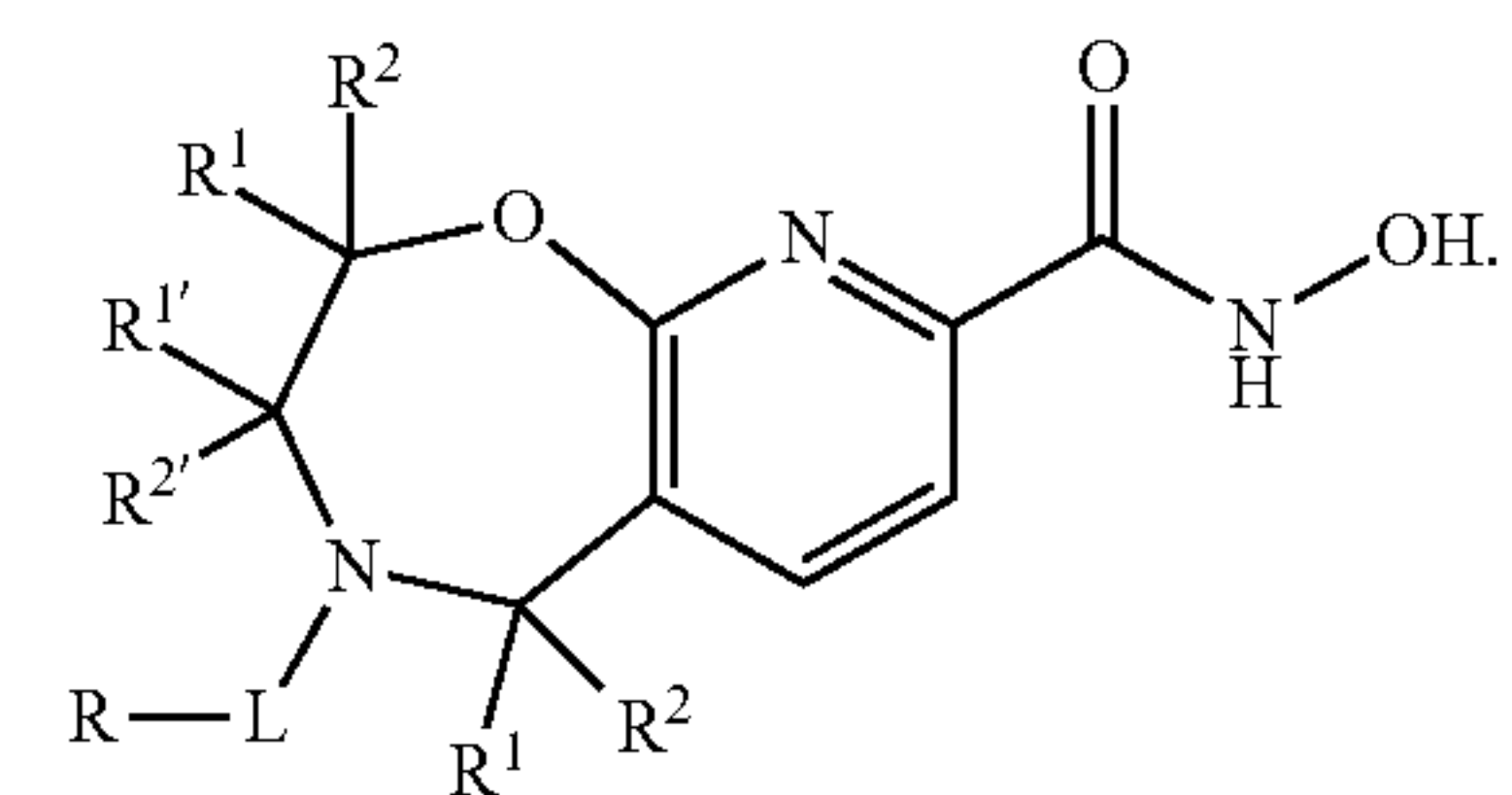


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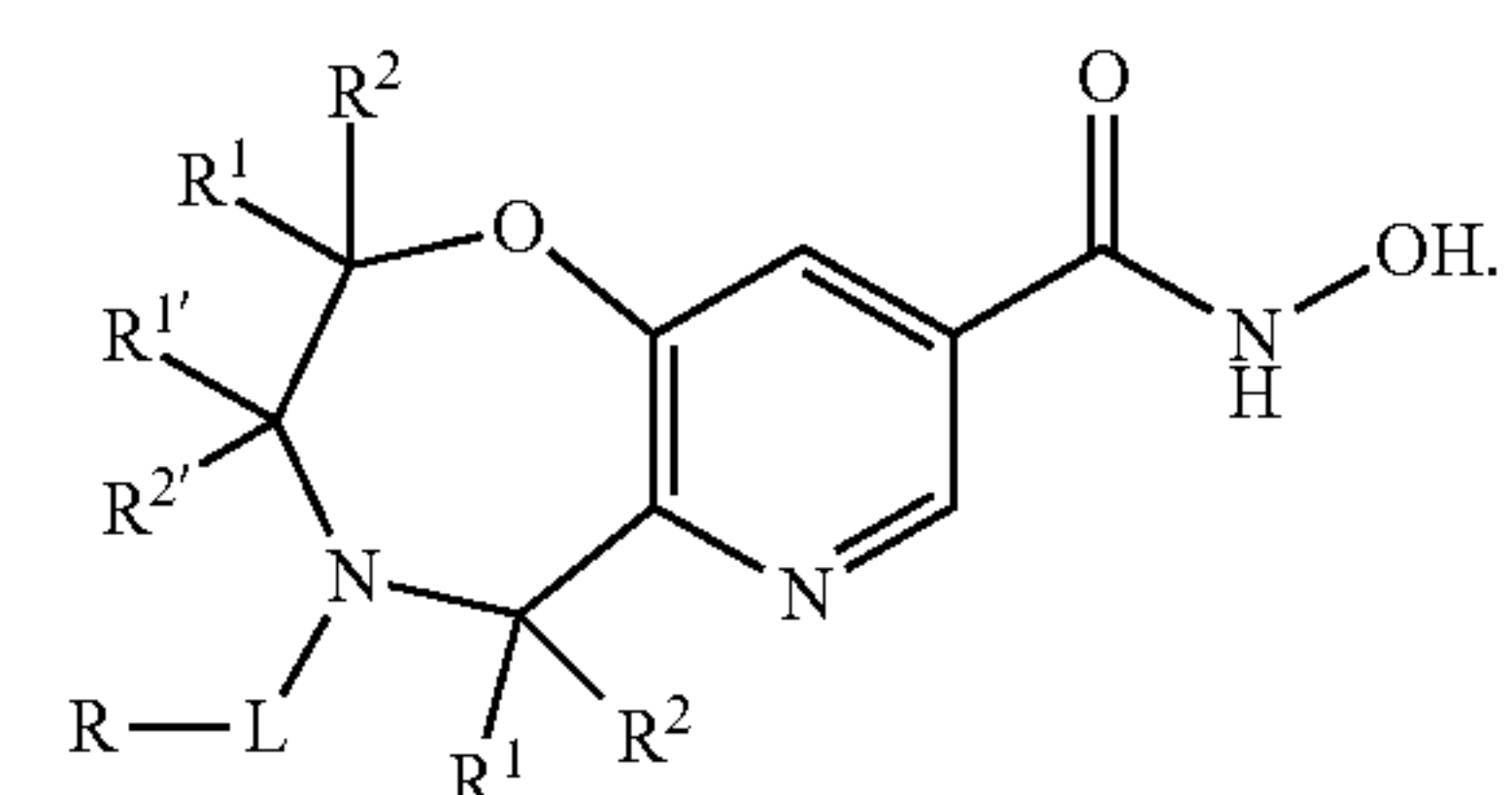
-continued



In other embodiments of the compounds of Formula IA, the compound is of the Formula IA-2:



In yet other another embodiments of the compounds of Formula IA, the compound is of the Formula IA-3:

**12**

In yet other embodiments of the compounds of Formula IA, the compound is of the Formula IA-4:

(IA-1c)

5

(IA-1d)

10

15

(IA-1e)

20

(IA-1f)

30

35

40

(IA-2)

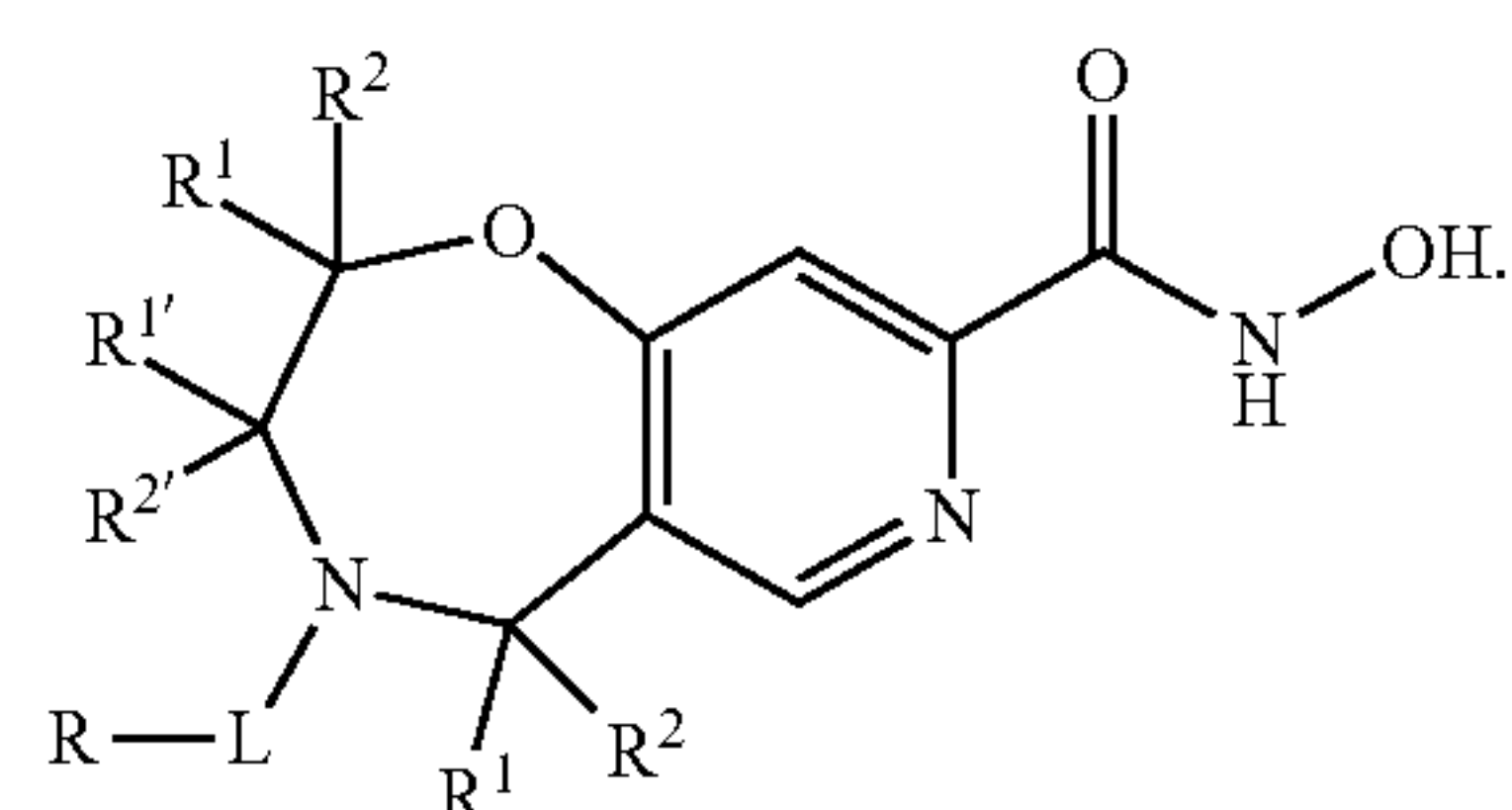
45

50

(IA-3)

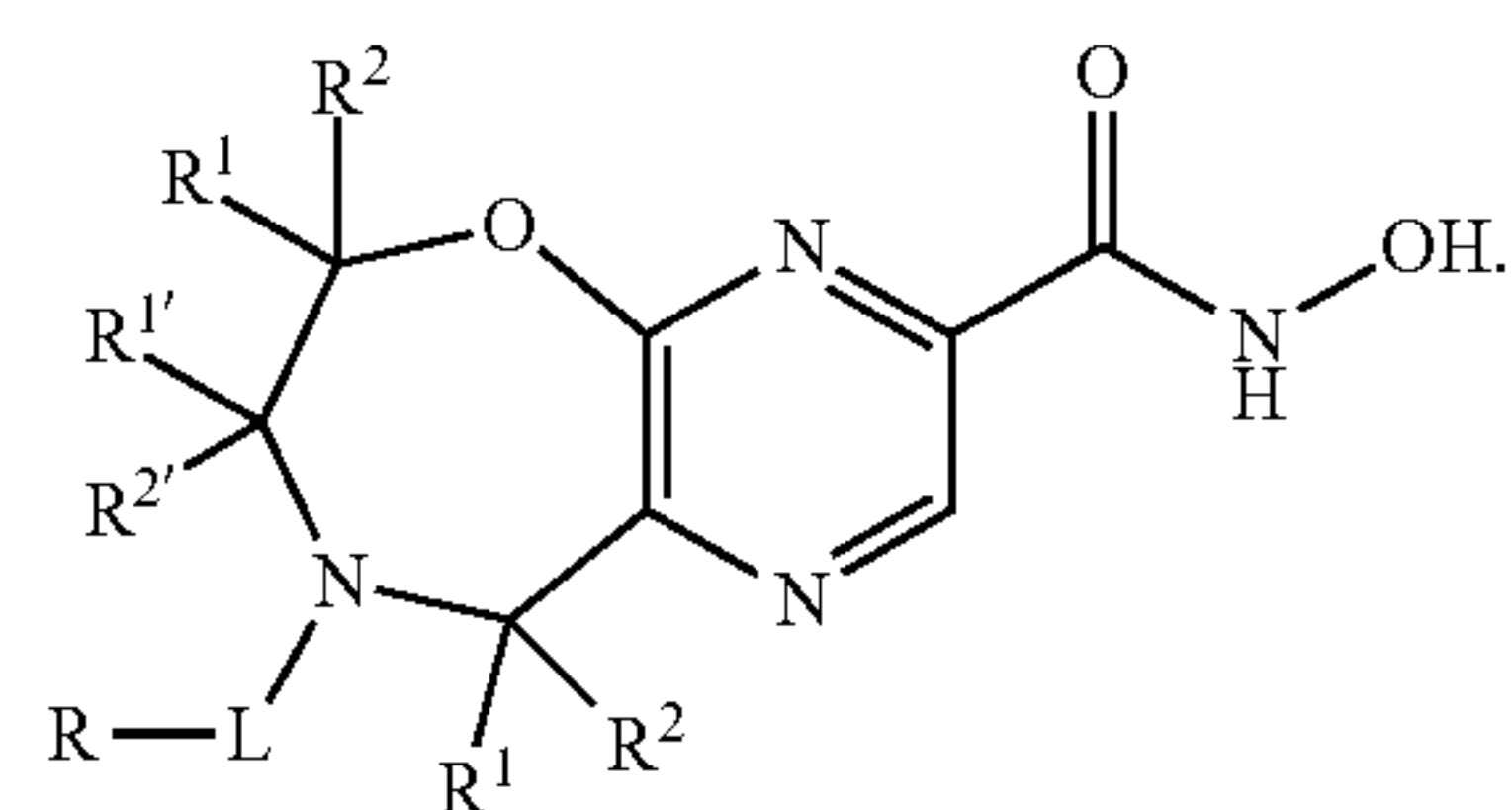
60

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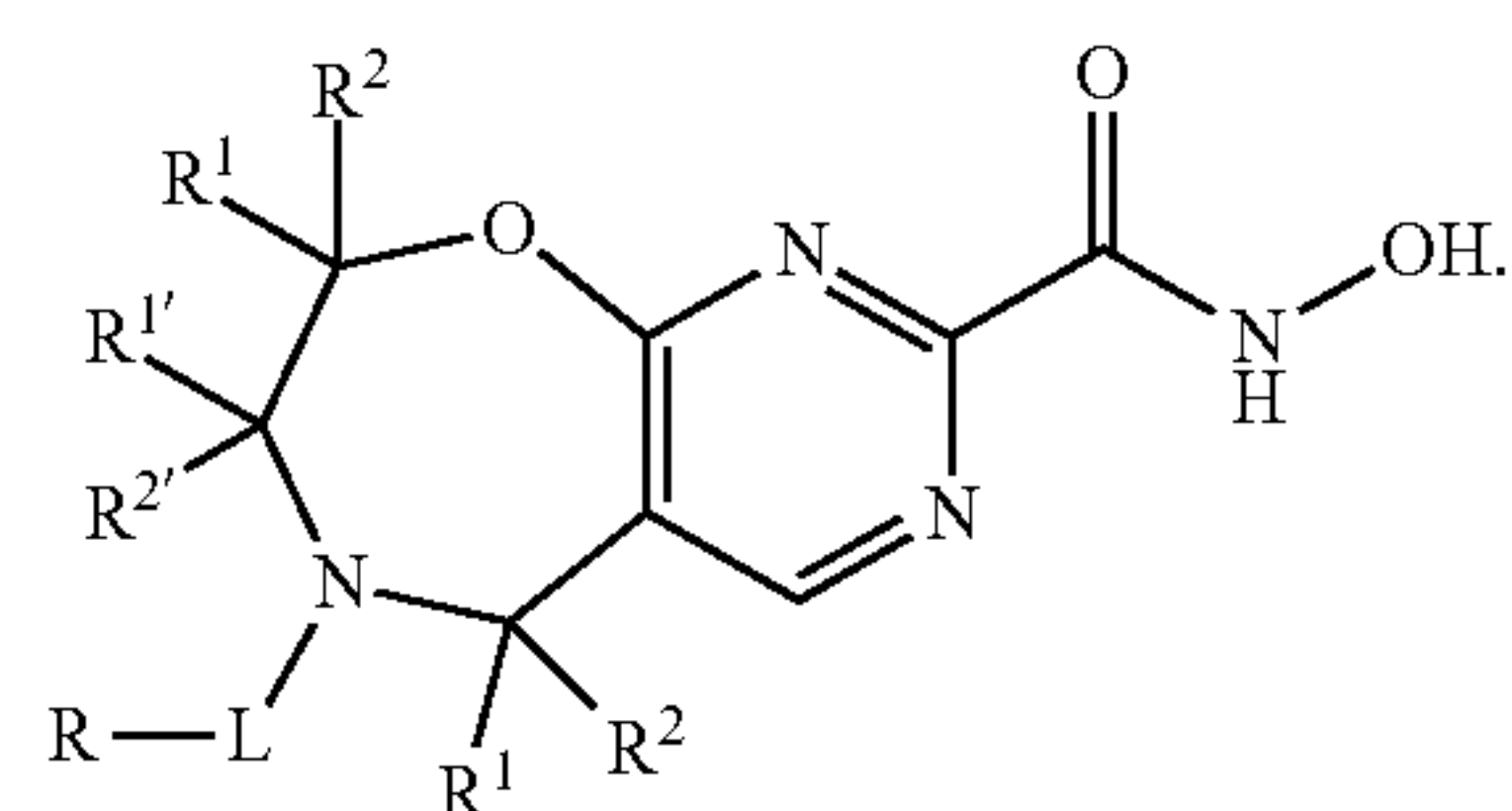
(IA-4)

In yet other another embodiments of the compounds of Formula IA, the compound is of the Formula IA-5:



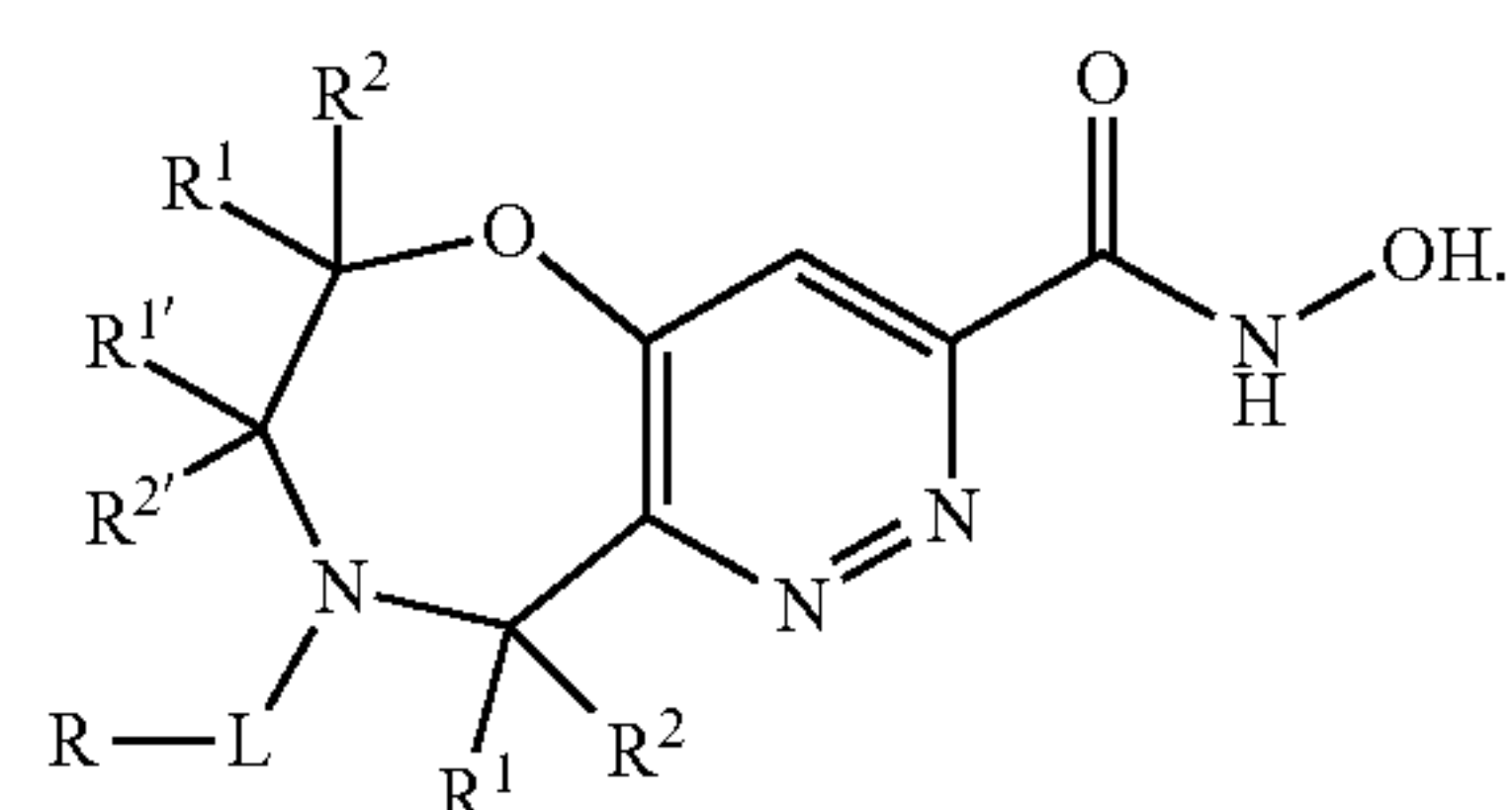
(IA-5)

In yet other another embodiments of the compounds of Formula IA, the compound is of the Formula IA-6:



(IA-6)

In yet other another embodiments of the compounds of Formula IA, the compound is of the Formula IA-7:

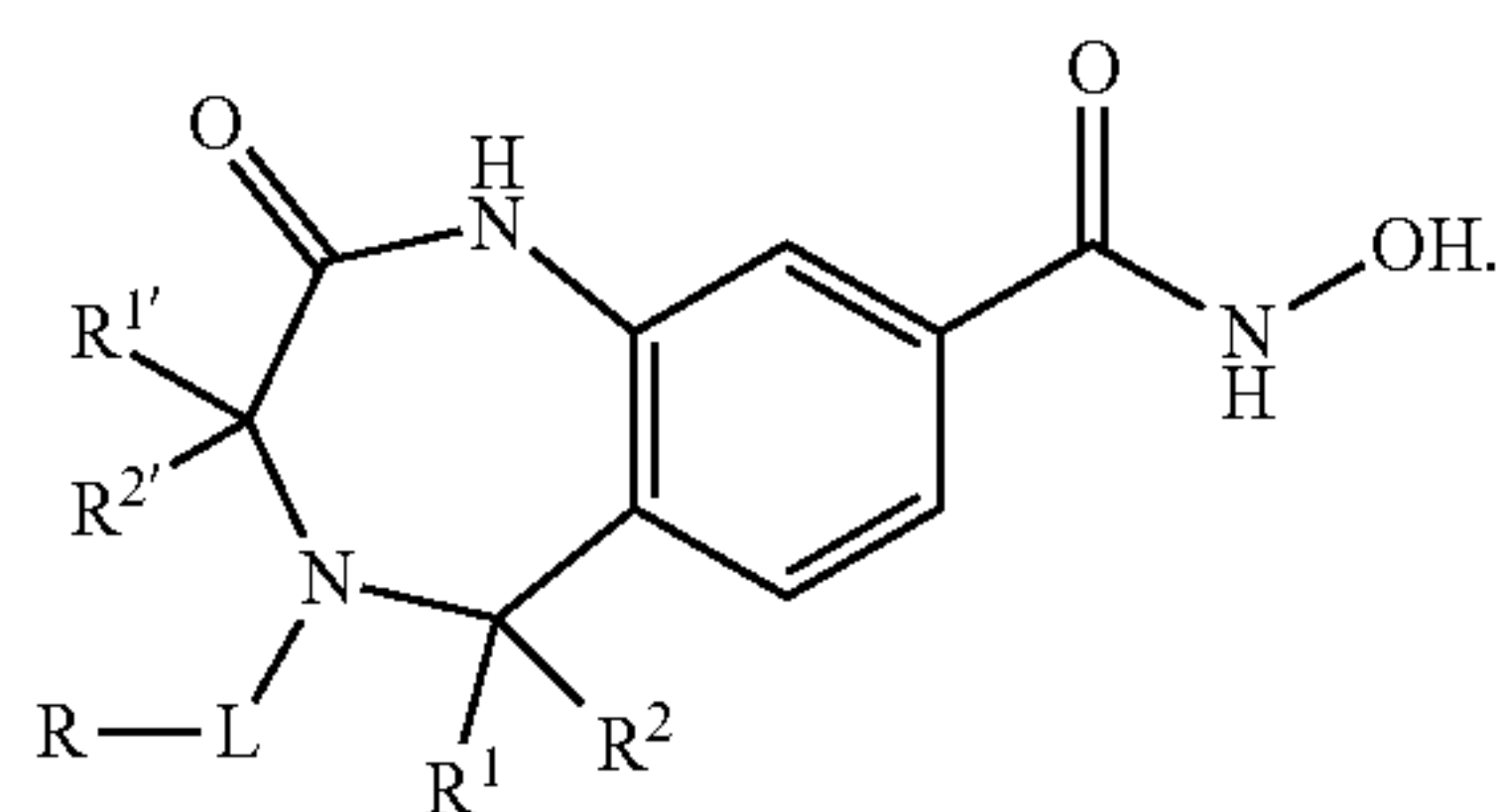


(IA-7)

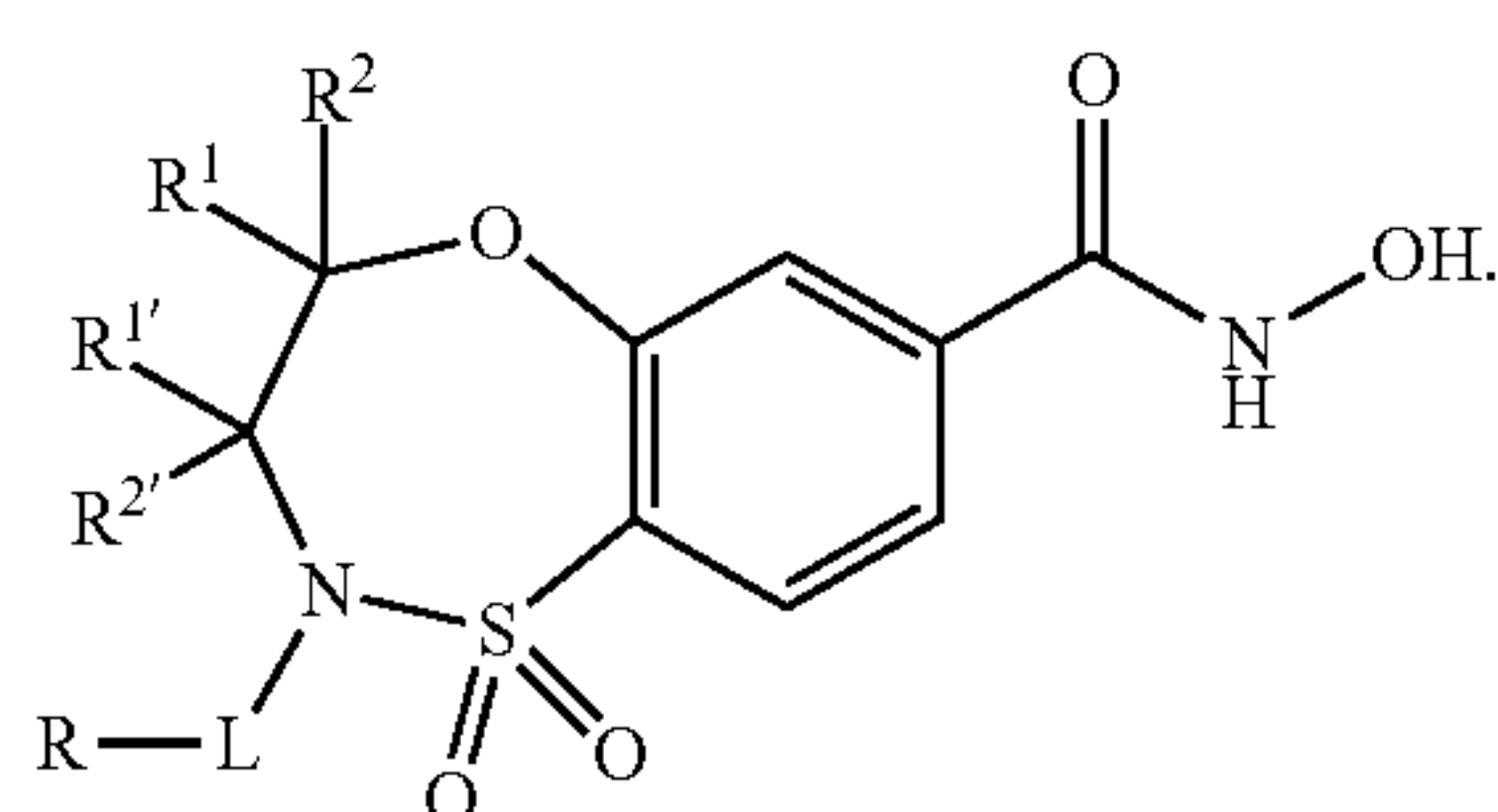


## 13

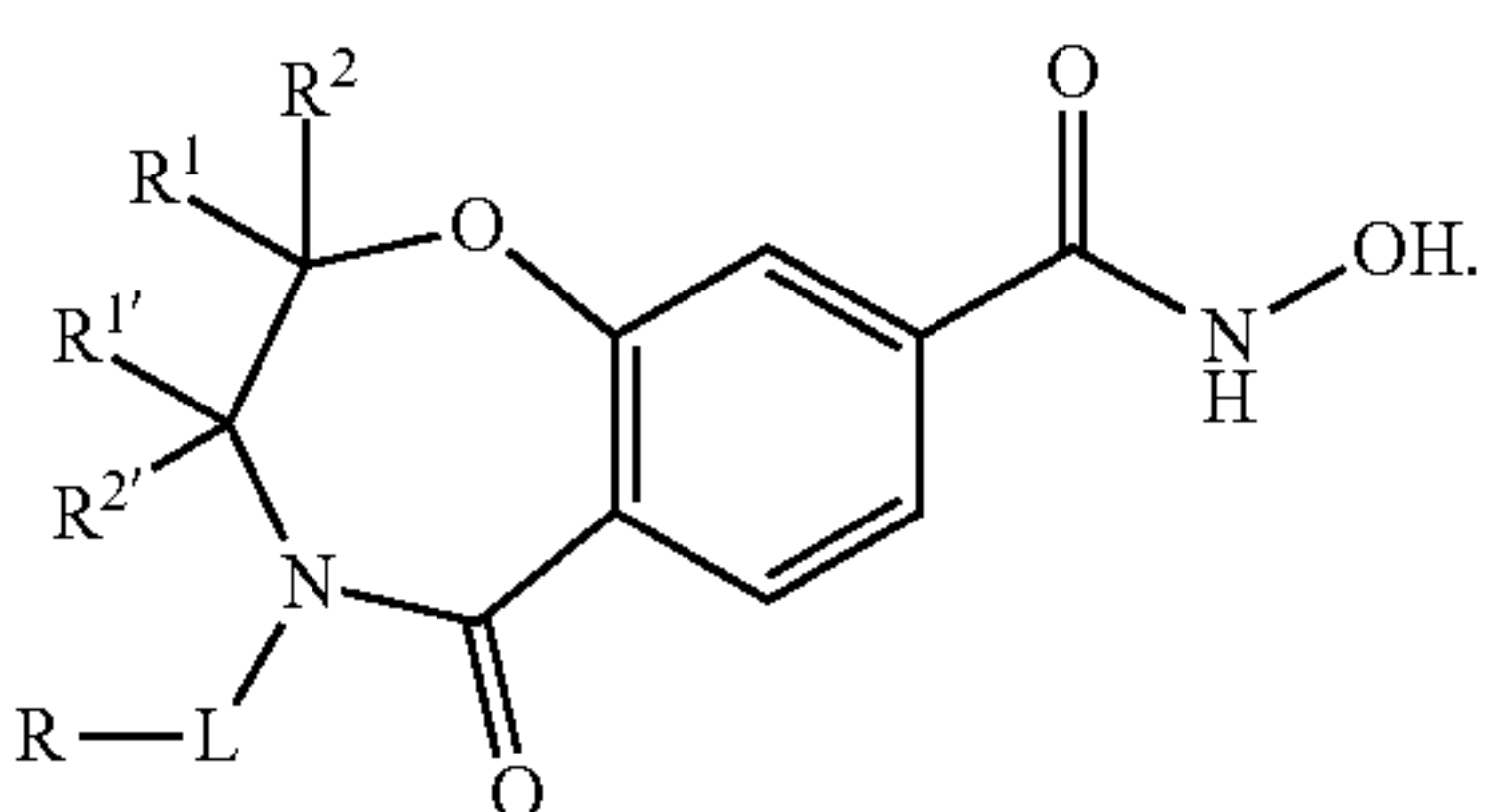
In other embodiments of the compounds of Formula IA, the compound may also be of the Formula IA-8:



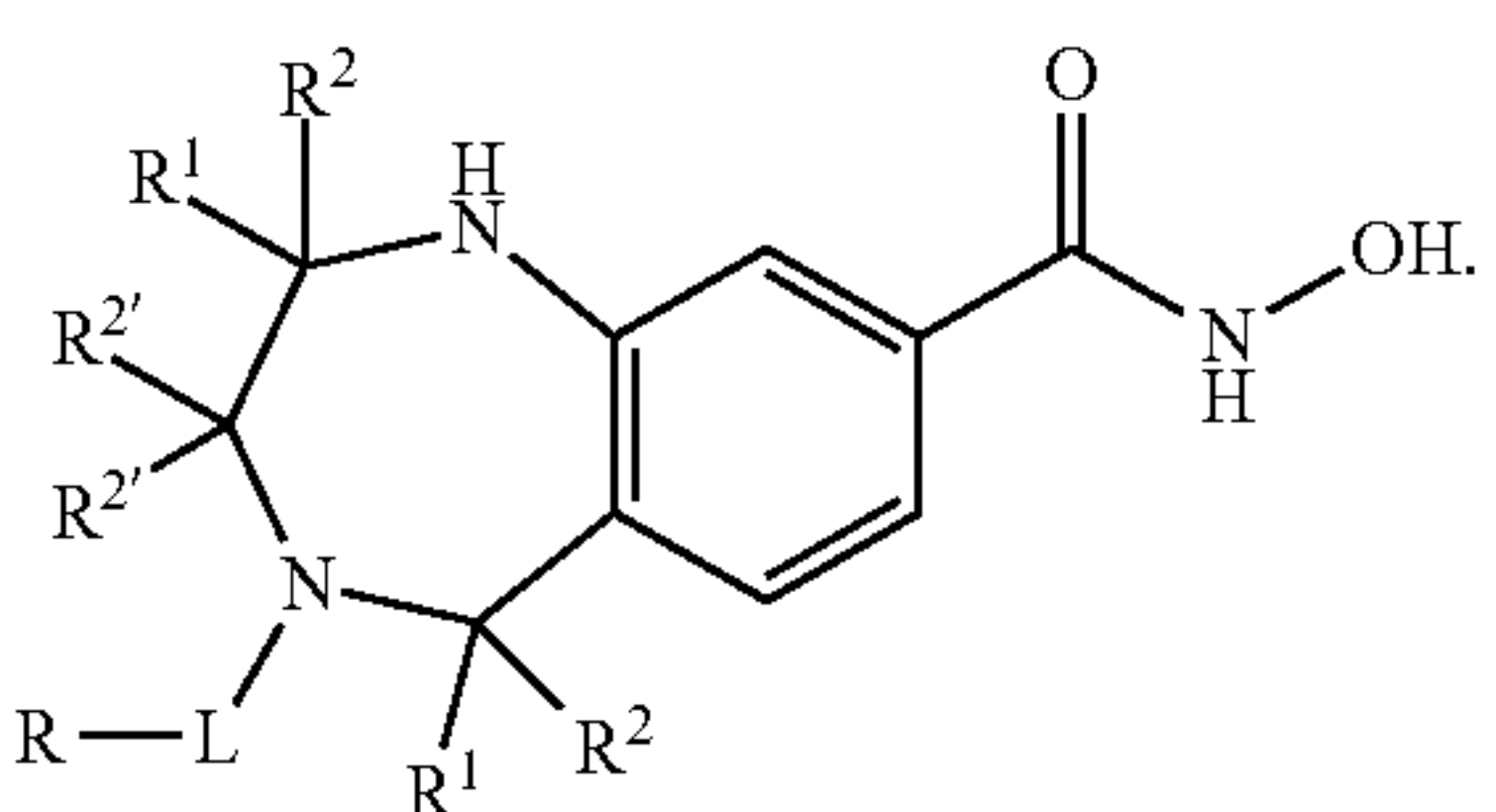
In other embodiments of the compounds of Formula IA, the compound is of the Formula IA-9:



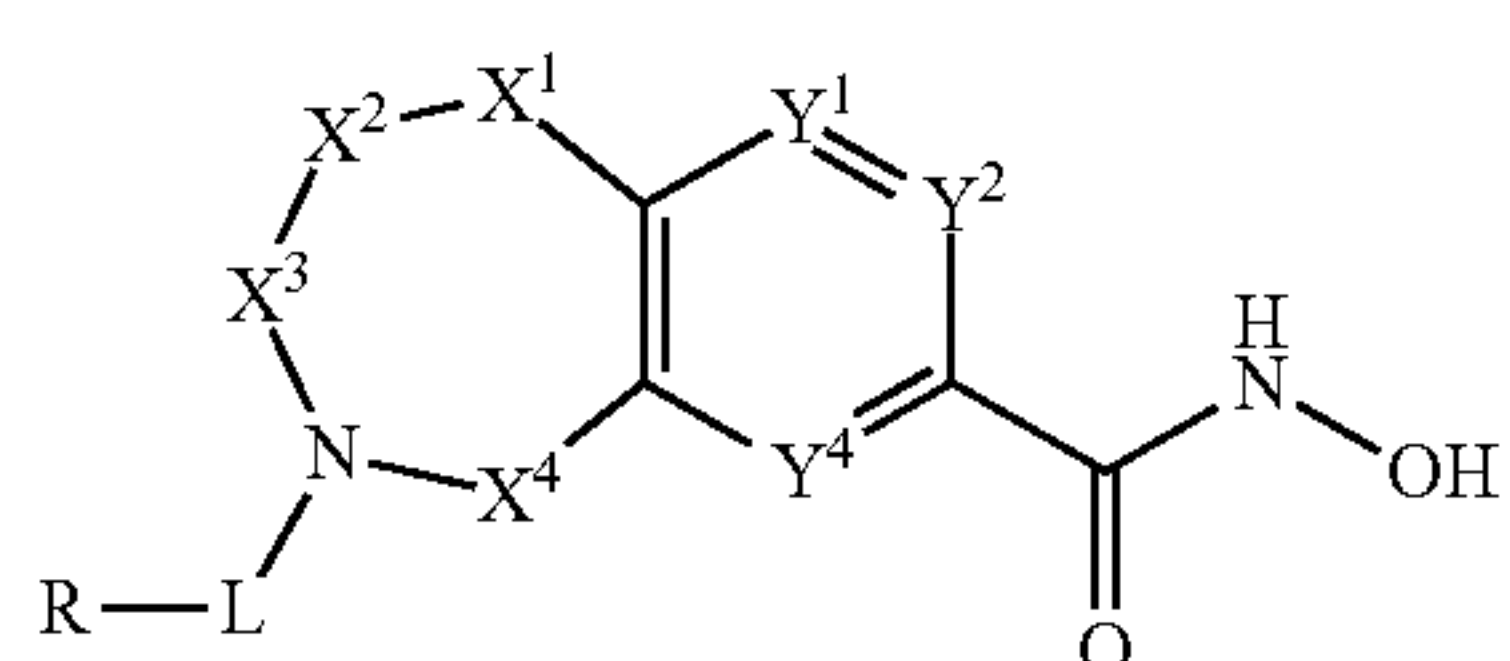
In a further embodiment of the compounds of Formula IA, the compound is also of the Formula IA-10:



In another embodiment of the compounds of Formula IA, the compound is of the Formula IA-11:



In one embodiment of the disclosure are also disclosed compounds of the Formula IB:



## 14

and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, enantiomers and isomers thereof where R, L, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, Y<sup>1</sup>, Y<sup>2</sup>, and Y<sup>4</sup> are defined as above in Formula I.

(IA-8) 5 In one embodiment of the compounds of Formula IB, X<sup>4</sup> is CR<sup>1</sup>R<sup>2</sup>.

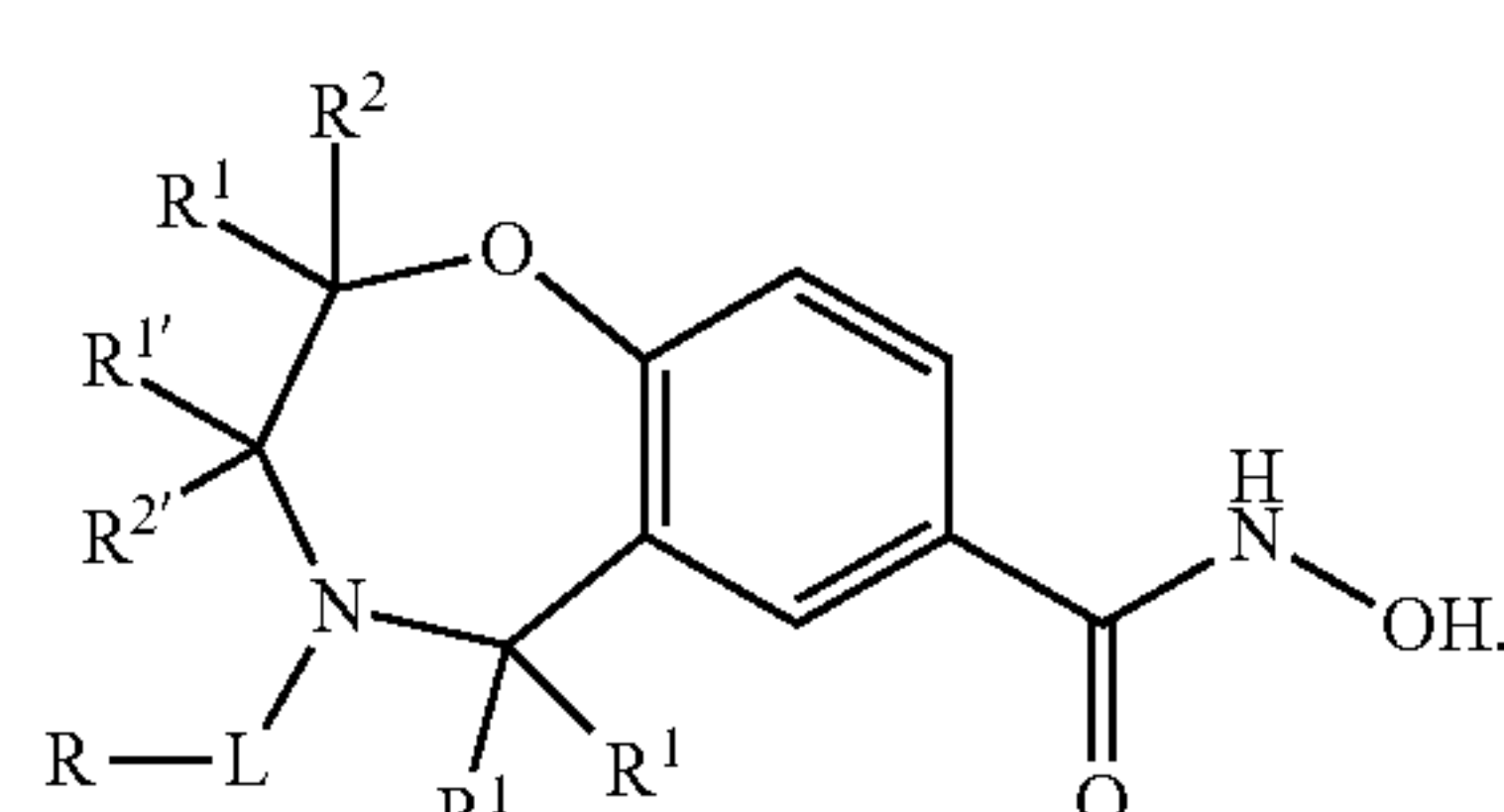
In another embodiment of the compounds of Formula IB, X<sup>1</sup> is NR<sup>3</sup>, O, or C=O.

10 In another embodiment of the compounds of Formula IB, X<sup>1</sup> is O.

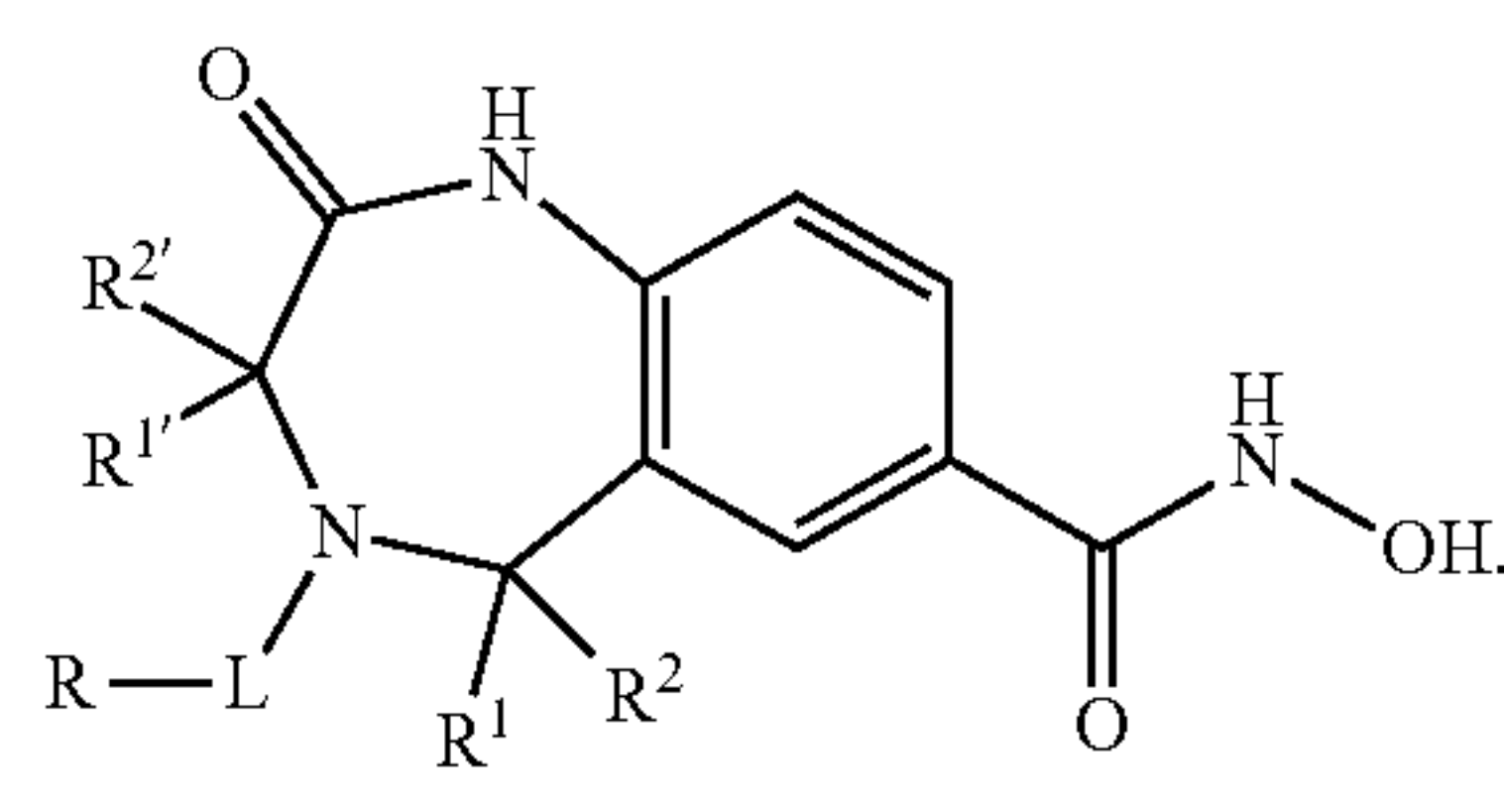
In another embodiment of the compounds of Formula IB, X<sup>1</sup> is O and X<sup>4</sup> is CR<sup>1</sup>R<sup>2</sup>.

In another embodiment of the compounds of Formula IB, X<sup>1</sup> is N, X<sup>2</sup> is C=O, and X<sup>4</sup> is CR<sup>1</sup>R<sup>2</sup>.

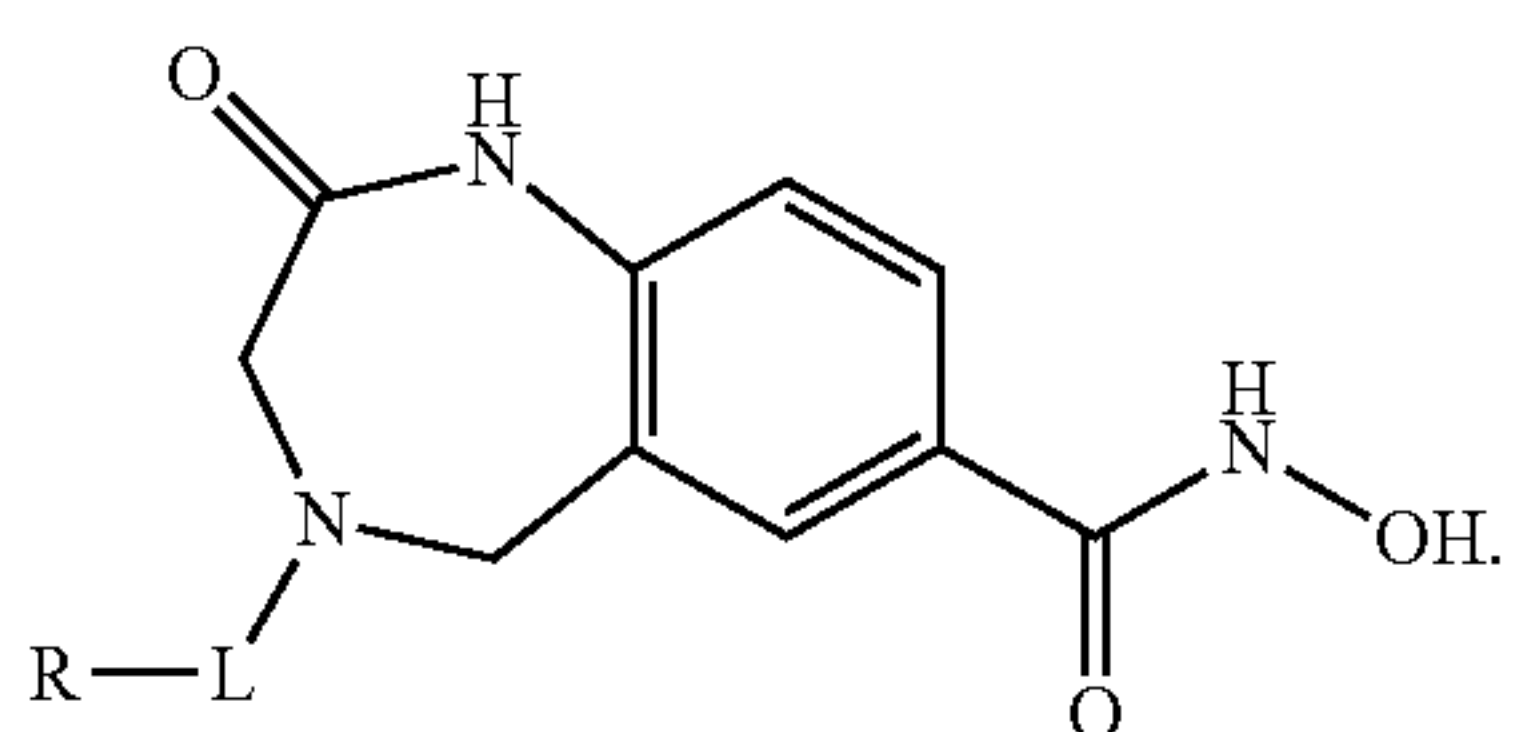
15 In some embodiments of the disclosure, the compounds of Formula IB, may be of the Formula IB-1:



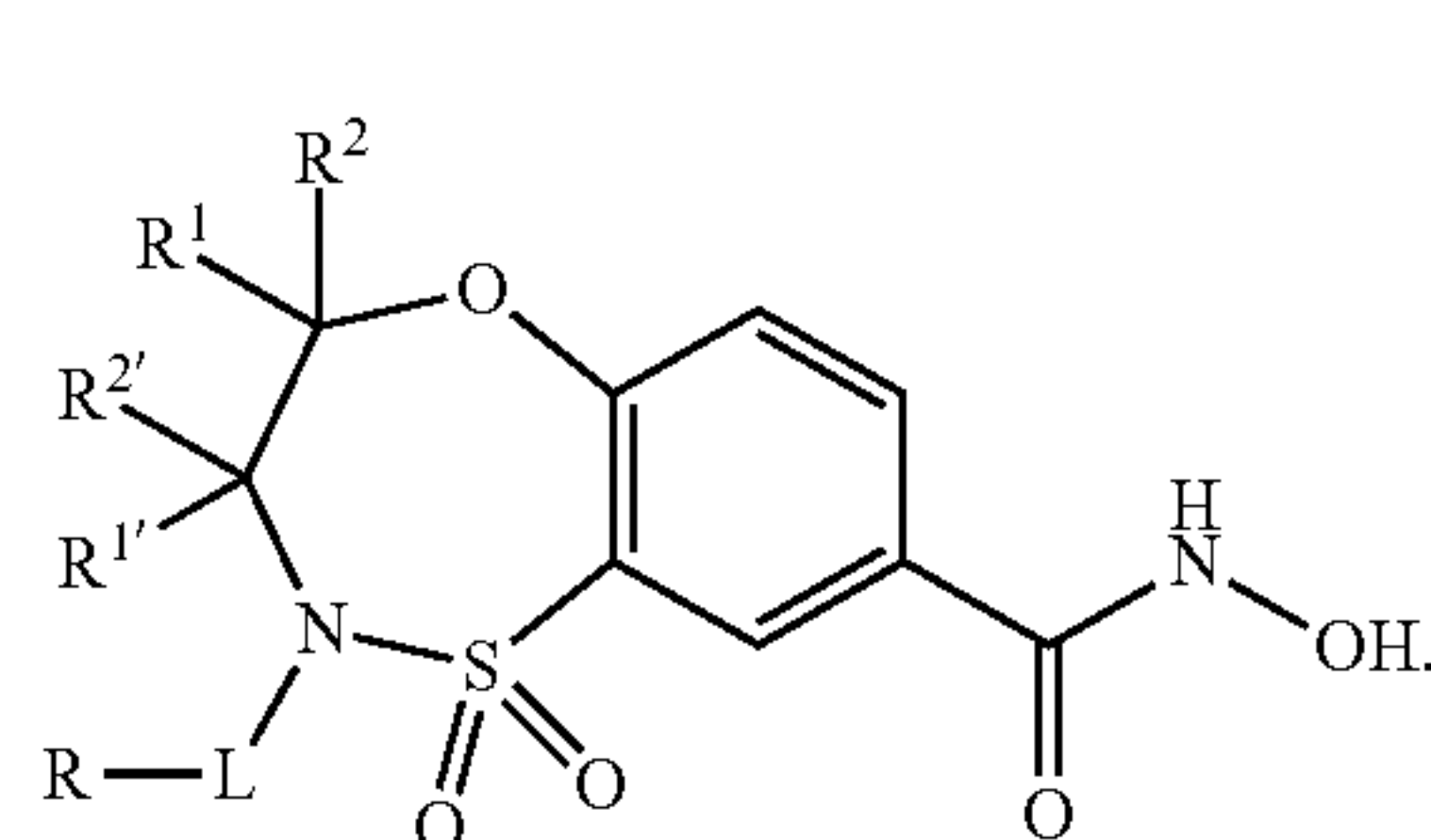
In other embodiments of the compounds of Formula IB, the compound is of the Formula IB-2:



For instance, in some embodiments, the compounds of the disclosure can be of the Formula IB-2a:



In yet other embodiments of the compounds of Formula IB, the compound is of the Formula (IB-3):

















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embodiment, R<sup>1</sup> and R<sup>2</sup>, when on adjacent atoms, combine to form a cycloalkyl. In yet another embodiment, R<sup>1</sup> and R<sup>2</sup>, when on adjacent atoms, combine to form a cycloalkenyl. In another embodiment, R<sup>1</sup> and R<sup>2</sup>, when on adjacent atoms, combine to form an aryl. In yet another embodiment, R<sup>1</sup> and R<sup>2</sup>, when on adjacent atoms, combine to form a heteroaryl containing 1 to 5 heteroatoms selected from the group consisting of N, S, P, and O.

In some embodiments of Formula (I), R<sup>1</sup> and R<sup>2</sup>, when on non-adjacent atoms, combine to form a bridging cycloalkyl. In yet another embodiment, R<sup>1</sup> and R<sup>2</sup>, when on non-adjacent atoms, combine to form a heterocycloalkyl.

In some embodiments of Formula (I), R<sup>1'</sup> and R<sup>2'</sup> combine with the atom to which they are both attached to form a spirocycle. In another embodiment, R<sup>1'</sup> and R<sup>2'</sup> combine with the atom to which they are both attached to form a spiroheterocycle. In another embodiment, R<sup>1</sup> and R<sup>2'</sup> combine with the atom to which they are both attached to form a spirocycloalkenyl.

In some embodiments of Formula (I), R<sup>1'</sup> and R<sup>2'</sup>, when on non-adjacent atoms, combine to form a bridging cycloalkyl. In yet another embodiment, R<sup>1'</sup> and R<sup>2'</sup>, when on non-adjacent atoms, combine to form a heterocycloalkyl.

In some embodiments of Formula (I), R<sup>3</sup> and R combine with the nitrogen atom to which they are attached to form a heterocycle optionally substituted with —R<sup>4</sup>, —OR<sup>4</sup>, or —NR<sup>4</sup>R<sup>5</sup>. In some embodiments of Formula (I), R<sup>3</sup> and R combine with the nitrogen atom to which they are attached to form a heteroaryl containing 1 to 5 heteroatoms selected from the group consisting of N, S, P, and O, optionally substituted with —R<sup>4</sup>, —OR<sup>4</sup>, or —NR<sup>4</sup>R<sup>5</sup>.

In some embodiments of Formula (I), n is 1 to 6. In another embodiment, n is 0 to 5. In yet another embodiment, n is 0 to 4. In yet another embodiment, n is 1 to 4. In another embodiment, n is 0 to 3. In yet another embodiment, n is 0 to 2. In yet another embodiment, n is 0 or 1. In another embodiment, n is 1 or 2.

In some embodiments of Formula (I), X<sup>4</sup>, X<sup>2</sup>, and X<sup>1</sup> are not all simultaneously CR<sup>1</sup>R<sup>2</sup>.

In some embodiments of Formula (I), X<sup>1</sup> is O, X<sup>2</sup> is CR<sup>1</sup>R<sup>2</sup>, and X<sup>4</sup> is CR<sup>1</sup>R<sup>2</sup>. In another embodiment, X<sup>2</sup> is C=O, X<sup>4</sup> is C=O, and X<sup>1</sup> is CR<sup>1</sup>R<sup>2</sup>. In yet another embodiment, X<sup>1</sup> is NR<sup>3</sup>, X<sup>2</sup> is C=O, and X<sup>4</sup> is CR<sup>1</sup>R<sup>2</sup>.

In an illustrative embodiment, the compound of Formula I is:

4-(benzo[d]oxazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
4-(1-(cyclohexylmethyl)-1H-benzo[d]imidazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
4-(benzo[d]thiazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
4-(cyclohexylmethyl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
4-(4-cyano-3-(trifluoromethyl)phenyl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
4-(3,4-dichlorophenyl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-4-(pyridin-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-4-(pyridin-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;

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N-hydroxy-4-(p-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
4-methoxyphenyl 8-(hydroxycarbamoyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate;  
cyclohexyl 8-(hydroxycarbamoyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate;  
N-hydroxy-4-(piperidin-1-yl sulfonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N8-hydroxy-N4-methyl-N4-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
4-cyclohexyl-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
4-(2-(dimethylamino)ethyl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-4-(2-methoxyethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-4-(1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(R)—N-hydroxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(R)—N8-hydroxy-N4-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
(R)—N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(R)—N-hydroxy-4-(4-methoxybenzyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(R)—N-hydroxy-2-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(R)—N-hydroxy-2,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(S)—N-hydroxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(S)—N8-hydroxy-N4-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
(S)—N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(S)—N-hydroxy-2-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(S)—N-hydroxy-2,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(S)—N-hydroxy-4-(4-methoxybenzyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-4-(4-methoxybenzyl)-3,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-3,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
N-hydroxy-3,3,4-trimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(R)—N-hydroxy-3-isopropyl-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(R)—N-hydroxy-3-isopropyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(R)—N8-hydroxy-3-isopropyl-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
(R)—N-hydroxy-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
(R)—N-hydroxy-3-isopropyl-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;



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(S)—N-hydroxy-3-isopropyl-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-isopropyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N8-hydroxy-3-isopropyl-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N-hydroxy-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-isopropyl-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (R)—N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (R)—N-hydroxy-3,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (R)—N8-hydroxy-N4-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (R)—N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (R)—N-hydroxy-4-(4-methoxybenzyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (R)—N-hydroxy-3-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N8-hydroxy-N4-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-4-(4-methoxybenzyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3,4-dimethyl-2,3,4,5-tetrahydrobenzo[1,4]oxazepine-8-carboxamide;  
 (R)—N-hydroxy-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 (S)—N-hydroxy-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 N8-hydroxy-N4-(4-methoxyphenyl)-2,3-dihydropyrido[2,3-f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxamide;  
 N8-hydroxy-N4-(4-methoxyphenyl)-2,3-dihydropyrido[3,2-f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(4-methoxybenzyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(4-methoxyphenethyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(4-methoxybenzyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 N-hydroxy-4-(4-methoxyphenethyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 N-hydroxy-4-(4-methoxyphenethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-8-carboxamide;  
 4-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-8-carboxamide;

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4-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-(4-methoxyphenethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(1-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-(4-methoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-(4-methoxybenzyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-(4-methoxybenzyl)-1-methyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 2-benzyl-N-hydroxy-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine-8-carboxamide 1,1-dioxide;  
 2-benzyl-N-hydroxy-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine-7-carboxamide 1,1-dioxide;  
 N8-hydroxy-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 N7-hydroxy-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,7(5H)-dicarboxamide;  
 N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 4-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 4-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 N-hydroxy-4-((1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-((1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 N-hydroxy-4-(4-methoxyphenethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(4-methoxyphenethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 4-(1H-benzo[d]imidazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 4-(1H-benzo[d]imidazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 N-hydroxy-4-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 N-hydroxy-4-((5-isopropylpyridin-2-yl)methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(pyridin-4-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(pyridin-2-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;



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N-hydroxy-2-oxo-4-(thiazol-2-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-(4-isopropoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(4-(trifluoromethoxy)benzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(3-phenoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(4-phenoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(3-(trifluoromethoxy)benzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(2-(trifluoromethoxy)benzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(4-(pyridin-2-yl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(4-(1H-pyrazol-1-yl)benzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(4-cyanobenzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(pyrimidin-5-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-(naphthalen-1-ylmethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-((2-(3-fluorophenyl)oxazol-4-yl)methyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(3-((dimethylamino)methyl)benzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-benzyl-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-(4-isopropylbenzyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(4-chlorobenzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(2,5-difluorobenzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(3,5-difluorobenzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(3,5-dichlorobenzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(2-fluoro-4-methoxybenzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(2-chlorobenzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-((2,2-difluorobenzo[d][1,3]dioxol-4-yl)methyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(pyridin-3-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-((1-methyl-1H-imidazol-2-yl)methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-((1-acetyl)piperidin-3-yl)methyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-(imidazo[1,2-a]pyridin-2-ylmethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(cyclopropylmethyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-((tetrahydrofuran-3-yl)methyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-((4,5-dimethylthiazol-2-yl)methyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;

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4-(3-chlorobenzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(4-(tert-butoxy)benzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 5 N-hydroxy-4-((1-isopropylpiperidin-4-yl)methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 4-(4-(1H-pyrrol-1-yl)benzyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 10 N-hydroxy-4-(naphthalen-2-ylmethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-4-((2-morpholinopyridin-4-yl)methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 15 N-hydroxy-4-(imidazo[1,2-a]pyridin-7-ylmethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 N-hydroxy-2-oxo-4-(4-(thiazol-2-yl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 20 N-hydroxy-4-((6-methoxypyridin-3-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-((6-methoxypyridin-3-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 25 N-hydroxy-4-((5-methoxypyridin-2-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-((5-methoxypyridin-2-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide;  
 (R)—N8-hydroxy-2-isopropyl-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 30 (R)—N8-hydroxy-2-(methoxymethyl)-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N8-hydroxy-2-(methoxymethyl)-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 35 (R)—N8-hydroxy-N4-(4-methoxyphenyl)-2-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N8-hydroxy-N4-(4-methoxyphenyl)-2-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 40 N-hydroxy-4-methyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxamide;  
 N-hydroxy-4-phenyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxamide;  
 45 N-hydroxy-4-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxamide;  
 (S)-3-ethyl-N-hydroxy-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 50 (S)-3-ethyl-N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-3-ethyl-N-hydroxy-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-3-ethyl-N-hydroxy-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 55 (S)—N-hydroxy-3-isopropyl-4-(pyridin-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-isopropyl-4-(pyridin-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 60 (S)—N-hydroxy-3-isopropyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-4-(2-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 65 (S)—N-hydroxy-3-methyl-4-(pyridin-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;



(S)—N-hydroxy-3-methyl-4-(pyrrolidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-4-(isoindoline-2-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-4-(4-methoxypiperidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-4-(4-methylpiperazine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (3 S)—N-hydroxy-3-methyl-4-(2-methylpiperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (3 S)—N-hydroxy-3-methyl-4-(3-methylmorpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-4-(oxetan-3-ylmethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(4-fluorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(3-fluorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-4-(4-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 methyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate;  
 isopropyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate;  
 (S)—N-hydroxy-3-methyl-4-(methylsulfonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(ethylsulfonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N8-hydroxy-N4,N4,3-trimethyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N-hydroxy-4-((2-methoxyethyl)sulfonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N8-hydroxy-N4-(2-methoxyethyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N8-hydroxy-3-methyl-N4-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N-hydroxy-3-methyl-4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N8-hydroxy-N4-(2-methoxyethyl)-N4,3-dimethyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N-hydroxy-3-methyl-4-(pyridin-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-4-(3-methoxypropyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (3 S)-4-(1-(4-fluorophenyl)ethyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-4-(3-morpholinopropyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (3 S)—N-hydroxy-3-methyl-4-(2-(tetrahydrofuran-2-yl)ethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-ethyl-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-4-isopropyl-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-4-isobutyl-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;

(S)-4-(cyclobutylmethyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(cyclopropylmethyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 5 (S)-4-(4-fluorobenzyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(cyclohexylmethyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 10 (S)—N-hydroxy-3-methyl-4-(2-morpholinoethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-4-(2-methoxyethyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(cyclopentylmethyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 15 (3 S)—N-hydroxy-3-methyl-4-((tetrahydrofuran-2-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-cyclopentyl-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 20 (S)-4-((4-fluorophenyl)sulfonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 cyclopentyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate;  
 25 cyclohexyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate;  
 (S)—N8-hydroxy-N4,3-dimethyl-N4-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 ethyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate;  
 30 cyclobutyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate;  
 tetrahydro-2H-pyran-4-yl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate;  
 35 4-fluorophenyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate;  
 (S)—N-hydroxy-3-methyl-4-(oxetan-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 40 (R)—N-hydroxy-3-(methoxymethyl)-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (R)—N-hydroxy-4-(4-methoxybenzyl)-3-(methoxymethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 45 (R)—N-hydroxy-3-(methoxymethyl)-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (R)—N-hydroxy-3-(methoxymethyl)-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-(methoxymethyl)-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 50 (S)—N-hydroxy-4-(4-methoxybenzyl)-3-(methoxymethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-(methoxymethyl)-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-(methoxymethyl)-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(pyrrolidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 60 N-hydroxy-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(4-methylpiperazine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(4-methoxypiperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 65 N-hydroxy-4-(isoindoline-2-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;



N-hydroxy-4-(2-methylpiperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-4-(3-methylmorpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (R)—N-hydroxy-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-4-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-3-methyl-4-(4-(trifluoromethoxy)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(4-chlorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(2-chlorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(2-fluorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(azetidine-1-carbonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N-hydroxy-4-(3-methoxyazetidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (3 S)—N-hydroxy-4-(3-methoxypyrrolidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)—N8-hydroxy-3-methyl-N4-(pyridin-3-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N4-cyclohexyl-N8-hydroxy-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N8-hydroxy-3-methyl-N4-(pyridin-2-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N8-hydroxy-3-methyl-N4-(tetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N8-hydroxy-N4,3-dimethyl-N4-(tetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)—N8-hydroxy-3-methyl-N4-(pyridin-4-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (S)-4-((1R,5R)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-((1 S,5 S)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (S)-4-(3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 N-hydroxy-2-oxo-4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide;  
 (S)-3-benzyl-N-hydroxy-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 In another embodiment, non-limiting illustrative compounds of the disclosure include:  
 N8-hydroxy-N4-(tetrahydro-2H-pyran-4-yl)-N4-(3-(trifluoromethyl)phenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide;  
 (R)—N-hydroxy-4-(morpholine-4-carbonyl)-3-((trifluoromethoxy)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide;  
 (3 S)—N-hydroxy-3,5-dimethyl-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide; or

(S)-6-fluoro-N-hydroxy-3-methyl-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide.

In another embodiment of the disclosure, the compounds of Formula I are enantiomers. In some embodiments the compounds are the (S)-enantiomer. In other embodiments the compounds are the (R)-enantiomer. In yet other embodiments, the compounds of Formula I may be (+) or (−) enantiomers.

It should be understood that all isomeric forms are included within the present disclosure, including mixtures thereof. If the compound contains a double bond, the substituent may be in the E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans configuration. All tautomeric forms are also intended to be included.

#### Methods of Synthesizing the Disclosed Compounds

The compounds of the present disclosure may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the schemes given below.

The compounds of Formula I may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes and examples. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles or chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of compounds of Formula I.

Those skilled in the art will recognize if a stereocenter exists in the compounds of Formula I. Accordingly, the present disclosure includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes.

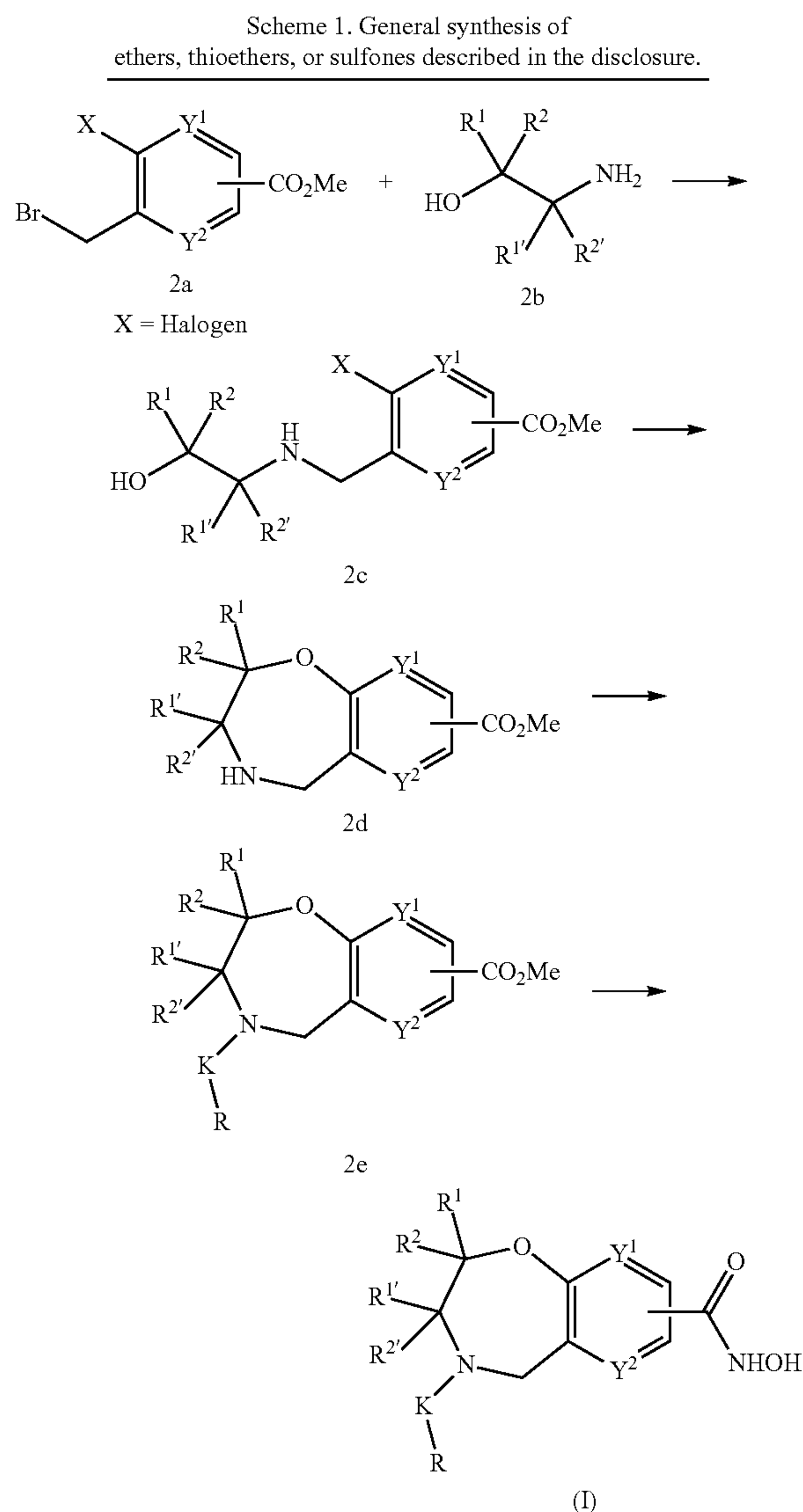
#### Preparation of Compounds

The compounds of the present disclosure can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present disclosure can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. These methods include, but are not limited, to those methods described below. Compounds of the present disclosure can be synthesized by following the steps outlined in General Schemes 1, 2, 3, 4, and 5 which comprise different sequences of assembling intermediates 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2m, 2n, 2o, 2p, 2q, 2r, 2s, 2t, 2u, 2v, 2w, 2x, 2y, 2z, 2aa, 2bb,



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and 2cc. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated.

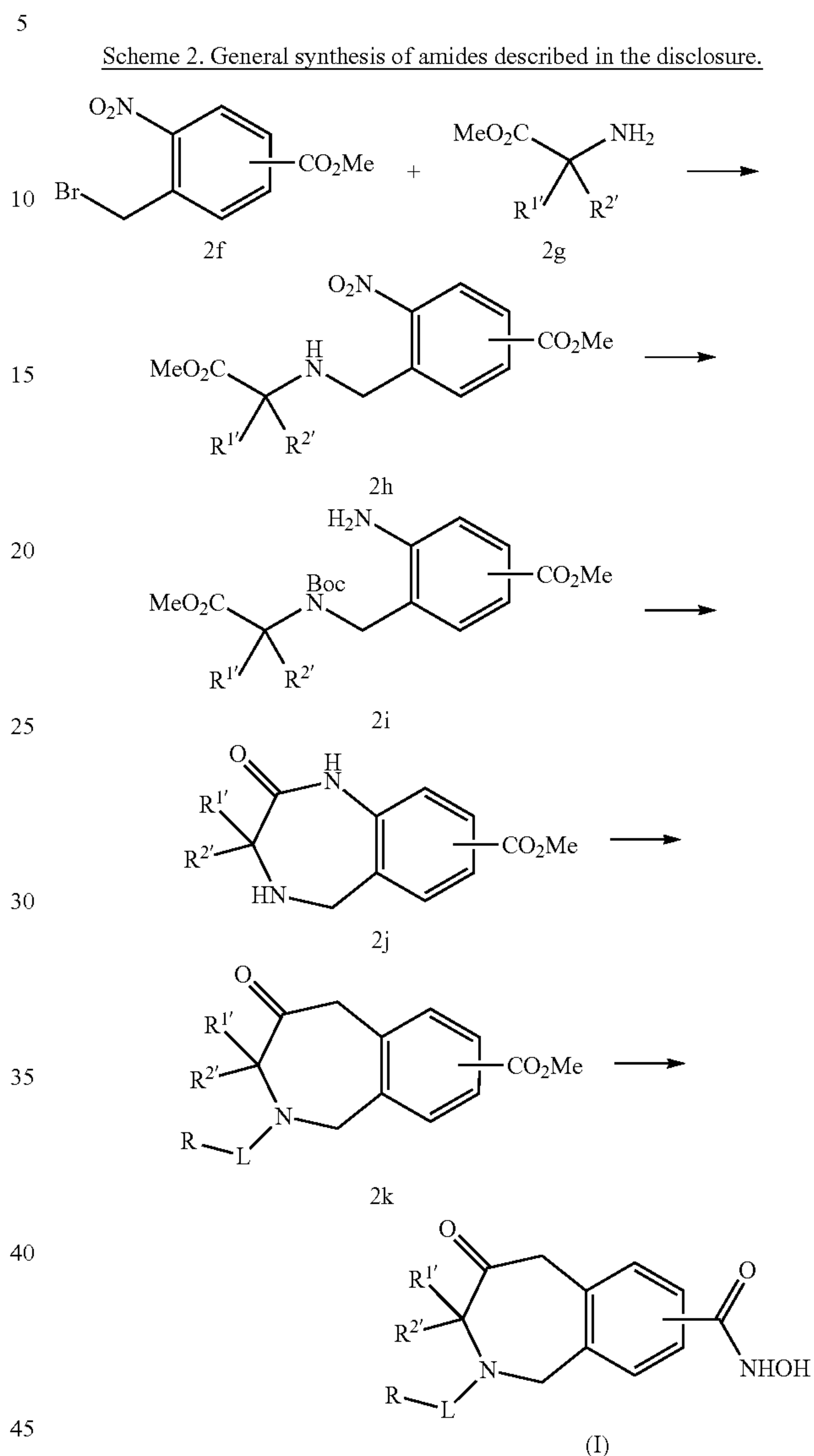


wherein L, R, R<sup>1</sup>, R<sup>2</sup>, R<sup>1'</sup>, R<sup>2'</sup>, Y<sup>1</sup> and Y<sup>2</sup> are defined as in Formula (I).

The general way of preparing target molecules of Formula (I) by using intermediates 2a, 2b, 2c, 2d, and 2e is outlined in General Scheme 1. Nucleophilic addition of alcohol 2b to Intermediate 2a using a base, e.g., potassium carbonate (K<sub>2</sub>CO<sub>3</sub>), in a solvent, e.g., acetonitrile (MeCN), provides Intermediate 2c. Cyclization of Intermediate 2c in the presence of a catalytic amount of a metal catalyst, e.g., copper iodide (CuI), palladium acetate (Pd(OAc)<sub>2</sub>), etc., and a base, e.g., potassium carbonate (K<sub>2</sub>CO<sub>3</sub>), in a solvent, e.g., isopropanol (i-PrOH), optionally at elevated temperature provides Intermediate 2d. Addition of the R-L moiety can be achieved, for instance, via alkylation, reductive amination, arylation, urea formation, or sulfonation. For example, alkylation of Intermediate 2d with an alkyl halide in the presence of a base, e.g., sodium hydride (NaH), and optionally at elevated temperatures provides Intermediate 2e. Treatment of Intermediate 2e with hydroxylamine and a base, e.g.,

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aqueous sodium hydroxide (aq. NaOH) in a solvent, e.g., tetrahydrofuran (THF) and/or methanol (MeOH), provides compounds of Formula (I).



wherein L, R, R<sup>1'</sup>, and R<sup>2'</sup> are defined as in Formula (I).

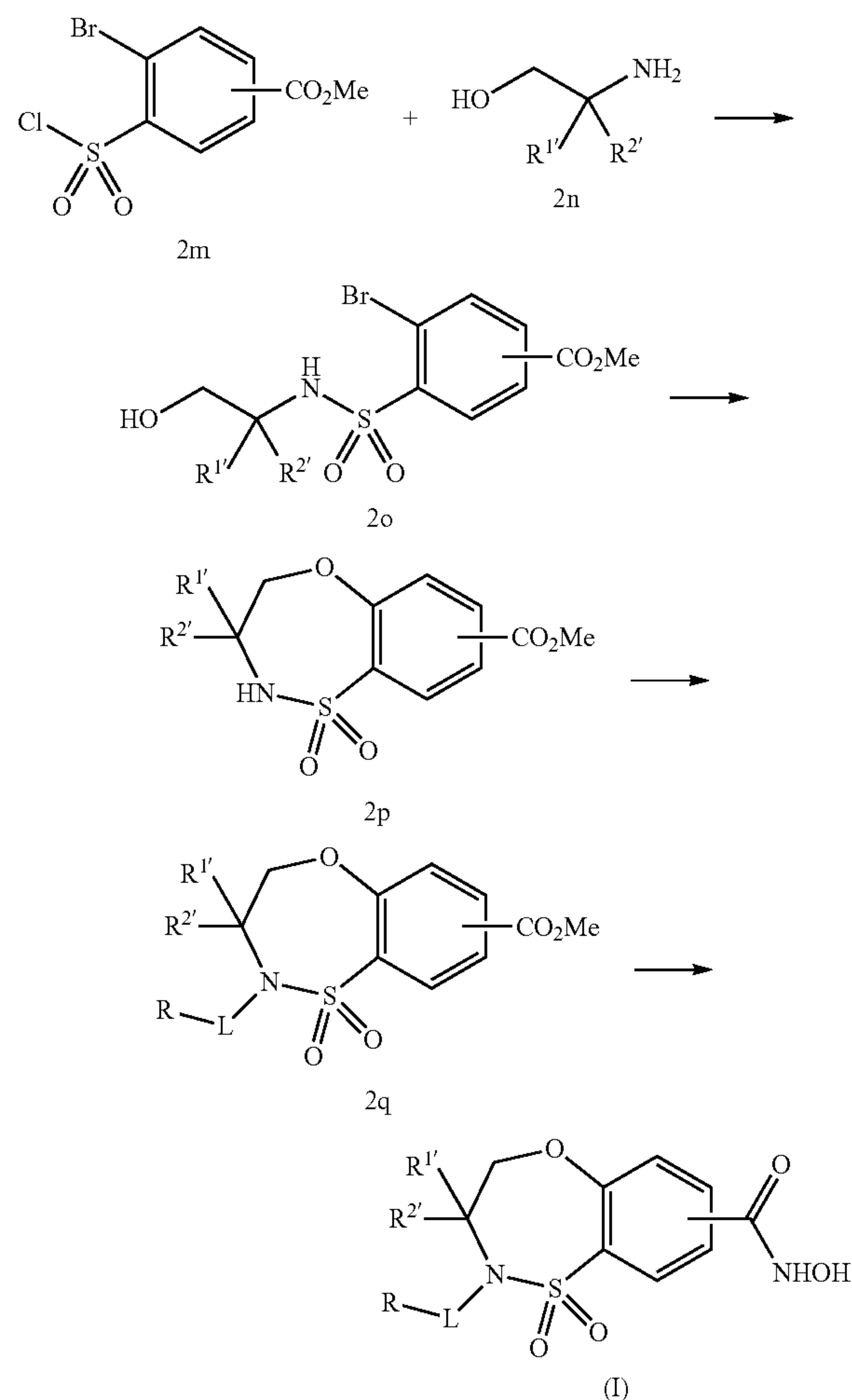
The general way of preparing target molecules of Formula (I) by using intermediates 2f, 2g, 2h, 2i, 2j, and 2k is outlined in General Scheme 2. Nucleophilic addition of amine 2g to Intermediate 2f using a base, e.g., N,N-diisopropylethylamine (DIEA), and in a solvent, e.g., MeCN, dichloromethane (DCM), or DMF, provides Intermediate 2h. Protection of the amine group in intermediate 2h with a typical acid labile protecting group (e.g., t-butoxycarbonyl (Boc)) using a protecting group precursor and 4-Dimethylaminopyridine (DMAP), in a solvent e.g., DCM or tetrahydrofuran (THF), followed by hydrogenation in the presence of a metal catalyst, e.g., palladium on carbon, and hydrogen (H<sub>2</sub>) gas in a solvent, e.g., DCM, provides Intermediate 2i. Cyclization of Intermediate 2i in the presence of a base, e.g., potassium carbonate (K<sub>2</sub>CO<sub>3</sub>), and in a solvent, e.g., isopropanol (i-PrOH), optionally at elevated temperatures provides Intermediate 2j. Addition of the R-L moiety can be achieved via alkylation, reductive amination, arylation, urea formation, or sulfonation. For example, alkylation of Intermediate 2j with



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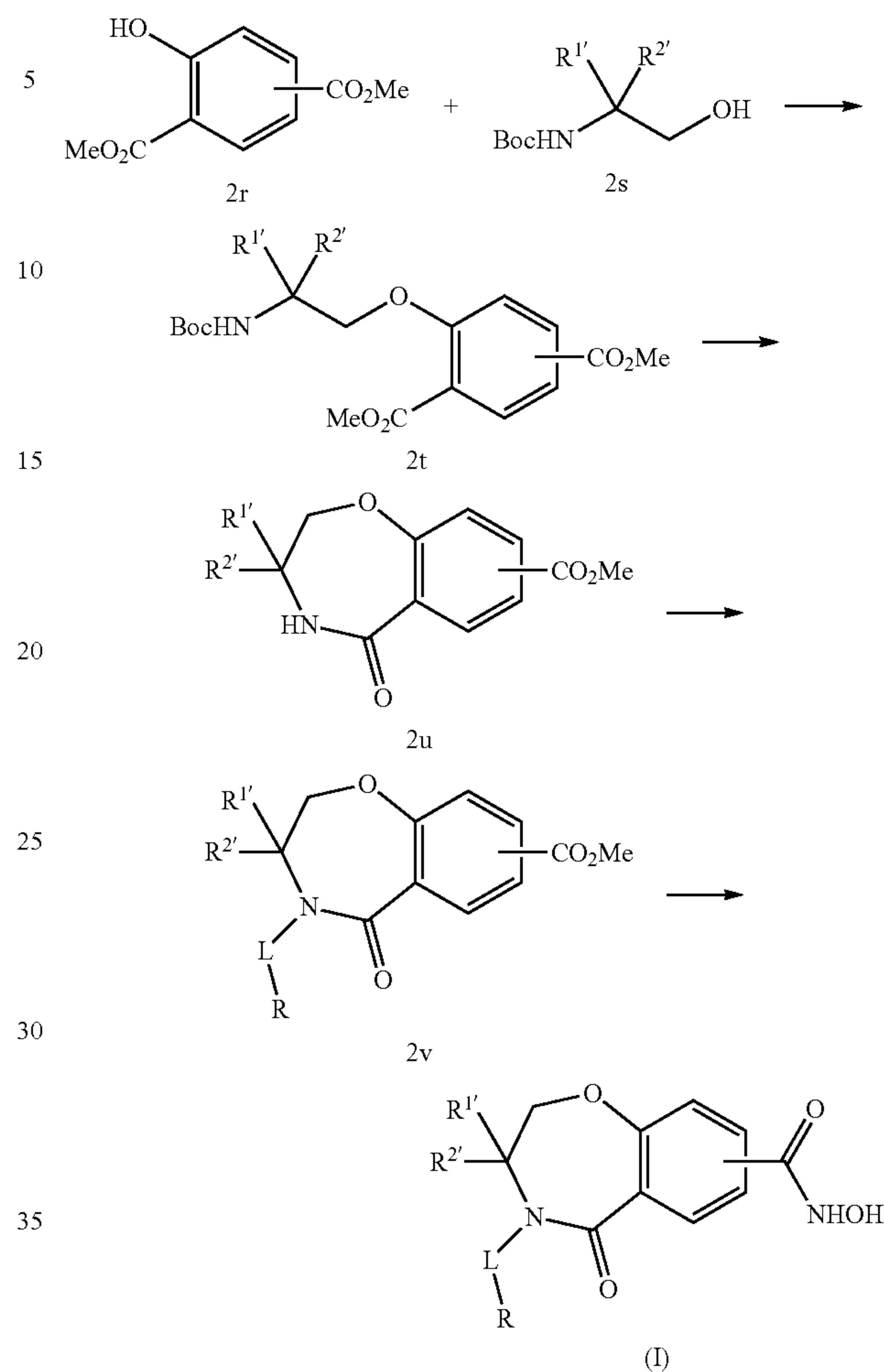
an alkyl halide in the presence of a base, e.g., sodium hydride (NaH), and optionally at elevated temperatures provides Intermediate 2k. Treatment of Intermediate 2k with hydroxylamine and a base, e.g., aqueous sodium hydroxide (aq. NaOH) in a solvent, e.g., tetrahydrofuran (THF) and/or methanol (MeOH), provides compounds of Formula (I).

Scheme 3. General synthesis of sulfonamides described in the disclosure.



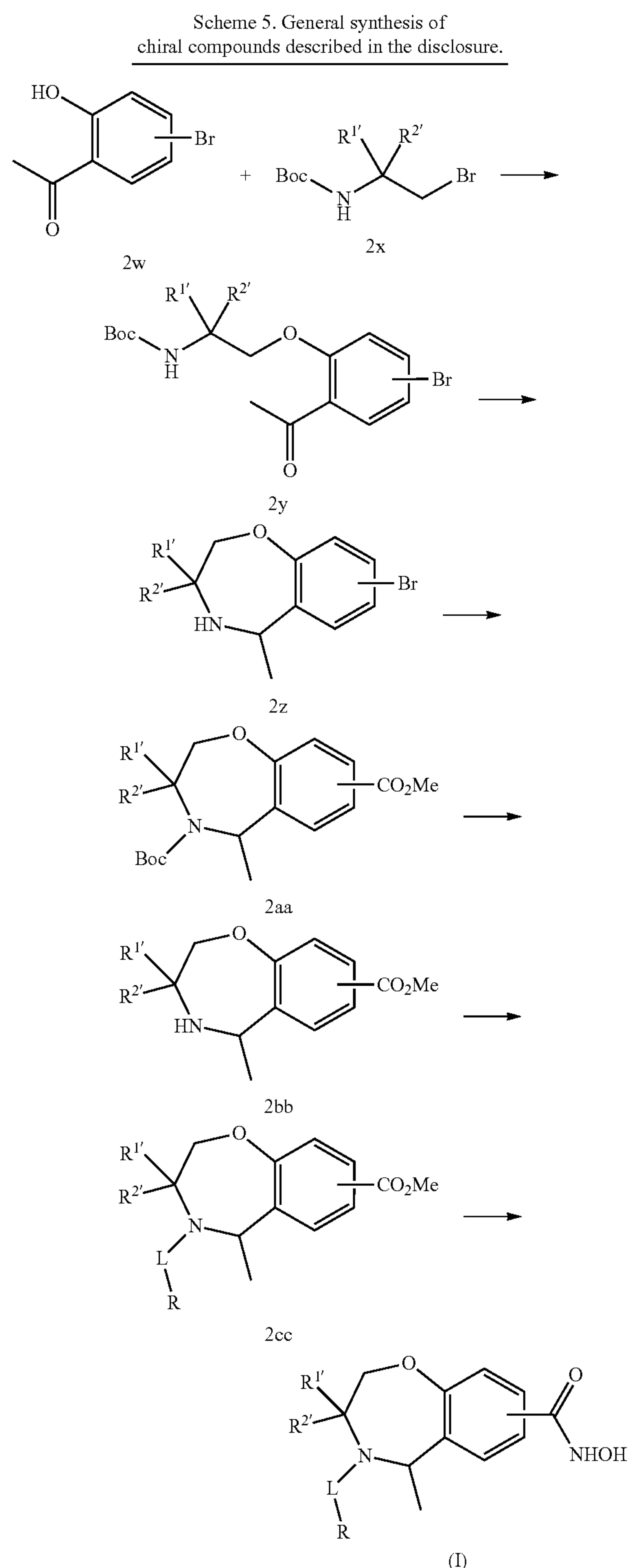
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Scheme 4. General synthesis of amides described in the disclosure.





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wherein L, R, R<sup>1'</sup>, and R<sup>2'</sup> are defined as in Formula (I).

The general way of preparing target molecules of Formula (I) by using intermediates 2w, 2x, 2y, 2z, 2aa, 2bb, and 2cc, is outlined in General Scheme 5. Alkylation of phenol 2w with Intermediate 2x using potassium iodide (KI) and a base, e.g., potassium carbonate (K<sub>2</sub>CO<sub>3</sub>), in a solvent, e.g., MeCN, THF, etc., provides Intermediate 2y. Deprotection of Intermediate 2y using a strong acid such as trifluoroacetic acid (TFA) in a solvent, e.g., dichloromethane (DCM) followed by cyclization via intramolecular reductive ami-

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nation in the presence of sodium borohydride or sodium cyanoborohydride in a solvent, e.g., THF, MeOH, etc., provides Intermediate 2z. Protection of the amine group in intermediate 2z with a typical acid labile protecting group (e.g., t-butoxycarbonyl (Boc)) using a protecting group precursor and optionally 4-DMAP in a solvent e.g., DCM or tetrahydrofuran (THF), followed by carbonylation in the presence of a metal catalyst, e.g., [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride, and carbon monoxide (CO) gas in a solvent, e.g., DCM, provides Intermediate 2aa. Deprotection of intermediate 2aa using a strong acid such as trifluoroacetic acid (TFA) in a solvent, e.g., dichloromethane (DCM) provides Intermediate 2bb. Addition of the R-L moiety can be achieved via alkylation, reductive amination, arylation, urea formation, or sulfonation. For example, alkylation of Intermediate 2bb with an alkyl halide in the presence of a base, e.g., sodium hydride (NaH), and optionally at elevated temperatures provides Intermediate 2cc. Treatment of Intermediate 2cc with hydroxylamine and a base, e.g., aqueous sodium hydroxide (aq. NaOH), in a solvent, e.g., tetrahydrofuran (THF) and/or methanol (MeOH), provides compounds of Formula (I).

#### Methods of Using the Disclosed Compounds

Another aspect of the disclosure relates to a method of treating a disease associated with HDAC, e.g., HDAC6, modulation in a subject in need thereof. The method involves administering to a patient in need of treatment for diseases or disorders associated with HDAC, e.g., HDAC6, modulation an effective amount of a compound of Formula I. In an embodiment, the disease can be, but is not limited to, cancer, neurodegenerative disease, neurodevelopmental disease, inflammatory or autoimmune disease, infection, metabolic disease, hematologic disease, or cardiovascular disease.

Another aspect of the disclosure is directed to a method of inhibiting an HDAC, e.g., HDAC6. The method involves administering to a patient in need thereof an effective amount of Formula I.

The present disclosure relates to compositions capable of modulating the activity of (e.g., inhibiting) HDACs, for instance HDAC6. The present disclosure also relates to the therapeutic use of such compounds.

One therapeutic use of the compounds of the present disclosure is to treat proliferative diseases or disorders such as cancer. Cancer can be understood as abnormal or unregulated cell growth within a patient and can include but is not limited to lung cancer, ovarian cancer, breast cancer, prostate cancer, pancreatic cancer, hepatocellular cancer, renal cancer and leukemias such as acute myeloid leukemia and acute lymphoblastic leukemia. Additional cancer types include T-cell lymphoma (e.g., cutaneous T-cell lymphoma, peripheral T-cell lymphoma), and multiple myeloma.

One therapeutic use of the compounds of the present disclosure is to treat neurological diseases or disorders or neurodegeneration. Neurological disorders are understood as disorders of the nervous system (e.g., the brain and spinal cord). Neurological disorders or neurodegenerative diseases can include but are not limited to epilepsy, attention deficit disorder (ADD), Alzheimer's disease, Parkinson's Disease, Huntington's Disease, amyotrophic lateral sclerosis, spinal muscular atrophy, essential tremor, central nervous system trauma caused by tissue injury, oxidative stress-induced neuronal or axonal degeneration, and multiple sclerosis.

Another therapeutic use of the compounds of the present disclosure is to treat neurodevelopmental disorders. Neurodevelopmental disorders can include, but are not limited to, Rett syndrome.



Another therapeutic use of the compounds of the present disclosure is also to treat inflammatory diseases or disorders. Inflammation can be understood as a host's response to an initial injury or infection. Symptoms of inflammation can include but are not limited to redness, swelling, pain, heat and loss of function. Inflammation may be caused by the upregulation of pro-inflammatory cytokines such as IL-1 $\beta$ , and increased expression of the FOXP3 transcription factor.

Another therapeutic use of the compounds of the present disclosure is also to treat autoimmune diseases or disorders. Autoimmune disorders are understood as disorders wherein a host's own immune system responds to tissues and substances occurring naturally in the host's body. Autoimmune diseases can include but are not limited to Rheumatoid arthritis, spondylitis arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease, graft versus host disease, transplant rejection, fibrotic disease, Crohn's Disease, type-1 diabetes, Eczema, and psoriasis.

Another therapeutic use of the compounds of the present disclosure is also to treat infectious diseases or disorders. Infections or infectious diseases are caused by the invasion of a foreign pathogen. The infection may be caused by, for instance, a bacteria, a fungus, or virus. For example, a bacterial infection may be caused by a *E. coli*.

Yet another therapeutic use of the compounds of the present disclosure is also to treat metabolic diseases or disorders. Metabolic diseases can be characterized as abnormalities in the way that a subject stores energy. Metabolic disorders can include but are not limited to metabolic syndrome, diabetes, obesity, high blood pressure, and heart failure.

Yet another therapeutic use of the compounds of the present disclosure is also to treat hematologic disorders. Hematologic diseases primarily affect the blood. Hematologic disorders can include but are not limited to anemia, lymphoma, and leukemia.

Yet another therapeutic use of the compounds of the present disclosure is also to treat cardiovascular diseases or disorders. Cardiovascular diseases affect the heart and blood vessels of a patient. Exemplary conditions include but are not limited to cardiovascular stress, pressure overload, chronic ischemia, infarction-reperfusion injury, hypertension, atherosclerosis, peripheral artery disease, and heart failure.

Another aspect of the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in treating or preventing a disease associated with HDAC6 modulation. In some embodiments, the disease is cancer, neurodegenerative disease, neurodevelopmental disorder, inflammatory or autoimmune disease, infection, metabolic disease, hematologic disease, or cardiovascular disease. In some embodiments, the compound inhibits a histone deacetylase. In another embodiment, the compound inhibits a zinc-dependent histone deacetylase. In another embodiment, the compound inhibits the HDAC6 isozyme zinc-dependent histone deacetylase.

In another aspect, the present disclosure relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating or preventing a disease associated with HDAC6 modulation. In some embodiments, the disease is cancer, neurodegenerative disease, neurodevelopmental disorder, inflammatory or autoimmune disease, infection, metabolic disease, hematologic disease, or cardiovascular disease. In

some embodiments, the compound inhibits a histone deacetylase. In another embodiment, the compound inhibits a zinc-dependent histone deacetylase. In another embodiment, the compound inhibits the HDAC6 isozyme zinc-dependent histone deacetylase.

In some embodiments, the cancer is cutaneous T-cell lymphoma, peripheral T-cell lymphoma, multiple myeloma, leukemia, lung, ovarian, breast, prostate, pancreatic, hepatocellular or renal cancer. In other embodiments, the neurodegenerative disease is Alzheimer's, Huntington's, Parkinson's, Amyotrophic Lateral Sclerosis, or spinal muscular atrophy. In other embodiments, the neurodevelopmental disorder is Rett syndrome. In yet other embodiments, the inflammatory or autoimmune disease is rheumatoid arthritis, spondylitis arthritis, psoriatic arthritis, psoriasis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel diseases, graft versus host disease, transplant rejection or fibrotic disease.

The disclosed compound can be administered in effective amounts to treat or prevent a disorder and/or prevent the development thereof in subjects.

Administration of the disclosed compounds can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

Depending on the intended mode of administration, the disclosed compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions, or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those skilled in the pharmaceutical arts.

Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising a Compound of the Disclosure and a pharmaceutically acceptable carrier, such as a) a diluent, e.g., purified water, triglyceride oils, such as hydrogenated or partially hydrogenated vegetable oil, or mixtures thereof, corn oil, olive oil, sunflower oil, safflower oil, fish oils, such as EPA or DHA, or their esters or triglycerides or mixtures thereof, omega-3 fatty acids or derivatives thereof, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) a lubricant, e.g., silica, talcum, stearic acid, its magnesium or calcium salt, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and/or polyethylene glycol; for tablets also; c) a binder, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone, if desired; d) a disintegrant, e.g., starches, agar, methyl cellulose, bentonite, xanthan gum, algiic acid or its sodium salt, or effervescent mixtures; e) absorbent, colorant, flavorant and sweetener; f) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcutoil, capmul MCM, capmul PG-12, captex 355, gelucire, vitamin E TGPS or other acceptable emulsifier; and/or g) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl-cyclodextrin, PEG400, PEG200.

Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For



example, the disclosed compound is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form an injectable isotonic solution or suspension. Proteins such as albumin, chylomicron particles, or serum proteins can be used to solubilize the disclosed compounds.

The disclosed compounds can be also formulated as a suppository that can be prepared from fatty emulsions or suspensions; using polyalkylene glycols such as propylene glycol, as the carrier.

The disclosed compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, containing cholesterol, stearylamine or phosphatidylcholines. In some embodiments, a film of lipid components is hydrated with an aqueous solution of drug to a form lipid layer encapsulating the drug, as described in U.S. Pat. No. 5,262,564.

Disclosed compounds can also be delivered by the use of monoclonal antibodies as individual carriers to which the disclosed compounds are coupled. The disclosed compounds can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspanami dephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the disclosed compounds can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels. In one embodiment, disclosed compounds are not covalently bound to a polymer, e.g., a polycarboxylic acid polymer, or a polyacrylate.

Parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

Another aspect of the disclosure relates to a pharmaceutical composition comprising a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier can further include an excipient, diluent, or surfactant.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1% to about 99%, from about 5% to about 90%, or from about 1% to about 20% of the disclosed compound by weight or volume.

The dosage regimen utilizing the disclosed compound is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal or hepatic function of the patient; and the particular disclosed compound employed. A physician or veterinarian of ordinary skill in the art can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Effective dosage amounts of the disclosed compounds, when used for the indicated effects, range from about 0.5 mg to about 5000 mg of the disclosed compound as needed to treat the condition. Compositions for in vivo or in vitro use

can contain about 0.5, 5, 20, 50, 75, 100, 150, 250, 500, 750, 1000, 1250, 2500, 3500, or 5000 mg of the disclosed compound, or, in a range of from one amount to another amount in the list of doses. In one embodiment, the compositions are in the form of a tablet that can be scored.

Without wishing to be bound by any particular theory, the compounds of the present disclosure can inhibit HDACs such as HDAC6 by interacting with the zinc ( $Zn^{2+}$ ) ion in the protein's active site via the hydroxamic acid group bound to the aromatic ring of the compound. The binding can prevent the zinc ion from interacting with its natural substrates, thus inhibiting the enzyme.

## EXAMPLES

The disclosure is further illustrated by the following examples and synthesis examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

The present disclosure includes a number of unique features and advantages compared with other inhibitors of HDAC enzymes, for instance HDAC6. For instance, the present disclosure features a unique class of small molecule therapeutic agents of Formula I. The compounds were designed by using crystal structure information of HDAC ligand-protein complexes as well as advanced computational chemistry tools. These techniques led to the development of new chemical scaffolds that were iteratively refined to optimize key recognition features between the ligand and receptor known to be necessary for potency.

Definitions used in the following examples and elsewhere herein are:

BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene

Boc: t-butoxycarbonyl

$CCl_4$ : carbon tetrachloride

$CDCl_3$ : deuterated chloroform

$CH_2Cl_2$ : methylene chloride, dichloromethane

CO (g): carbon monoxide gas

$Cs_2CO_3$ : cesium carbonate

$Cu(OAc)_2$  copper (II) acetate

CuI: copper (I) iodide

DEAD: diethyl azodicarboxylate

DIEA: diisopropylethylamine

DMA: dimethylacetamide

DMF: N,N-dimethylformamide

DMSO: dimethylsulfoxide

$Et_3N$ : triethylamine

$Et_2O$ : diethyl ether

EtOAc: EtOAc

h: hours

$H_2O$ : water

HCl: hydrochloric acid

$H_4NHCO_3$ : ammonium bicarbonate

Johnphos: (2-biphenyl)di-tert-butylphosphine

$K_2CO_3$ : potassium carbonate

$KH_2PO_4$  potassium dihydrogen phosphate

MeCN: acetonitrile

MeOH: methanol

$MgSO_4$ : magnesium sulfate

$NaBH(OAc)_3$ : sodium triacetoxyborohydride



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min: minutes

Na(CN)BH<sub>3</sub>: sodium cyanoborohydrideNa<sub>2</sub>SO<sub>4</sub>: sodium sulfateNaHCO<sub>3</sub>: sodium bicarbonate

NaOH: sodium hydroxide

NBS: N-bromosuccinimide

NH<sub>2</sub>OH: hydroxylamineNH<sub>4</sub>Cl: ammonium chlorideNH<sub>4</sub>HCO<sub>3</sub>: ammonium bicarbonatePd(dppf)Cl<sub>2</sub>: [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)Pd(dppf)Cl<sub>2</sub>.CH<sub>2</sub>Cl<sub>2</sub>: [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)-dichloromethane adductPd(OAc)<sub>2</sub>: palladium(II) acetatePd<sub>2</sub>(dba)<sub>3</sub> tris(dibenzylideneacetone)dipalladium(0)Pd<sub>2</sub>(dba)<sub>3</sub>.CHCl<sub>3</sub> tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct

pet. ether: petroleum ether

prep-HPLC: preparatory high pressure liquid chromatography

prep-TLC: preparatory thin layer chromatography

RuPhos 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl

RuPhos-Pd-G2 chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

TFA: trifluoroacetic acid

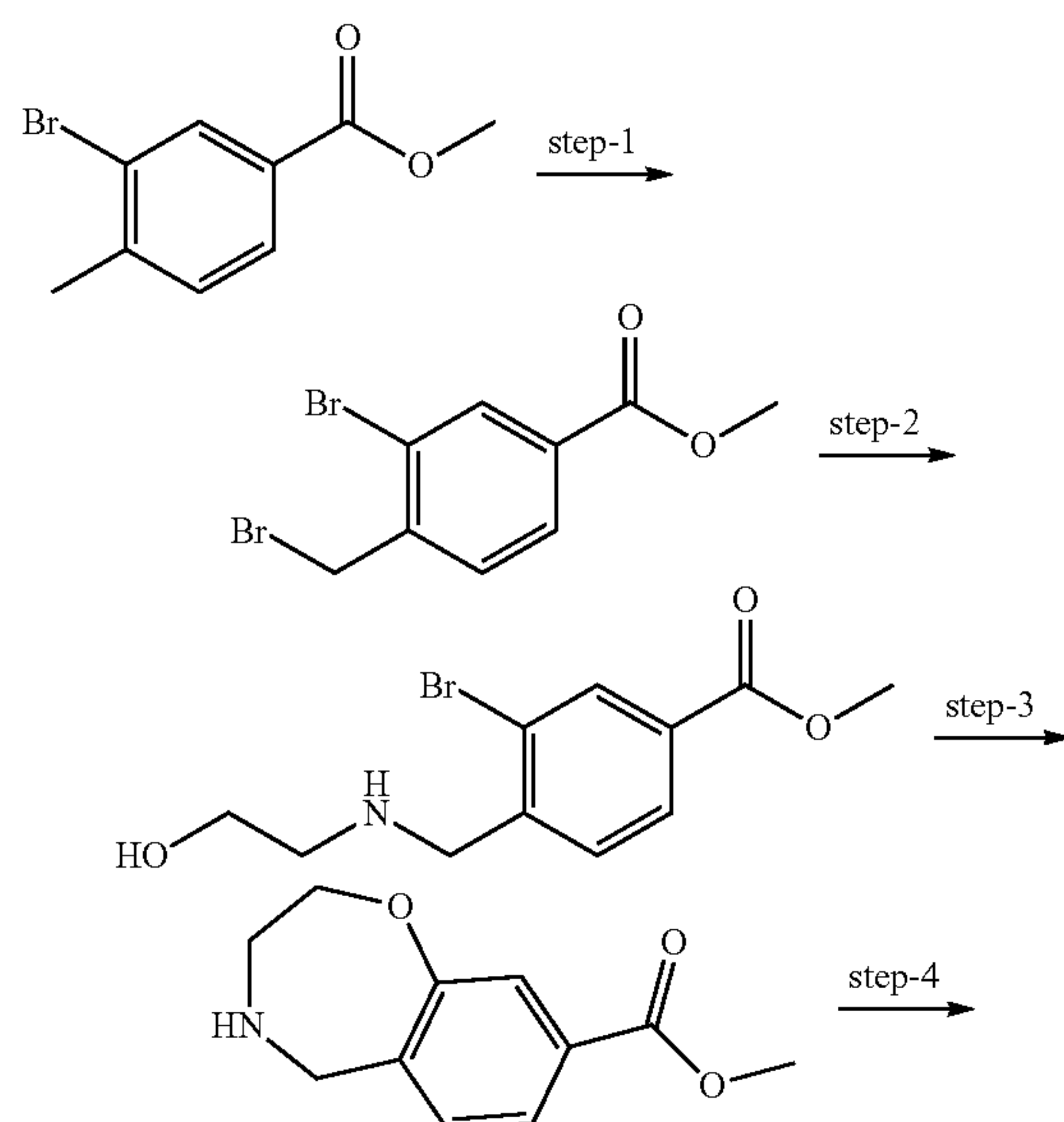
THF: tetrahydrofuran

Xantphos 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

XPhos-Pd-G3 (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

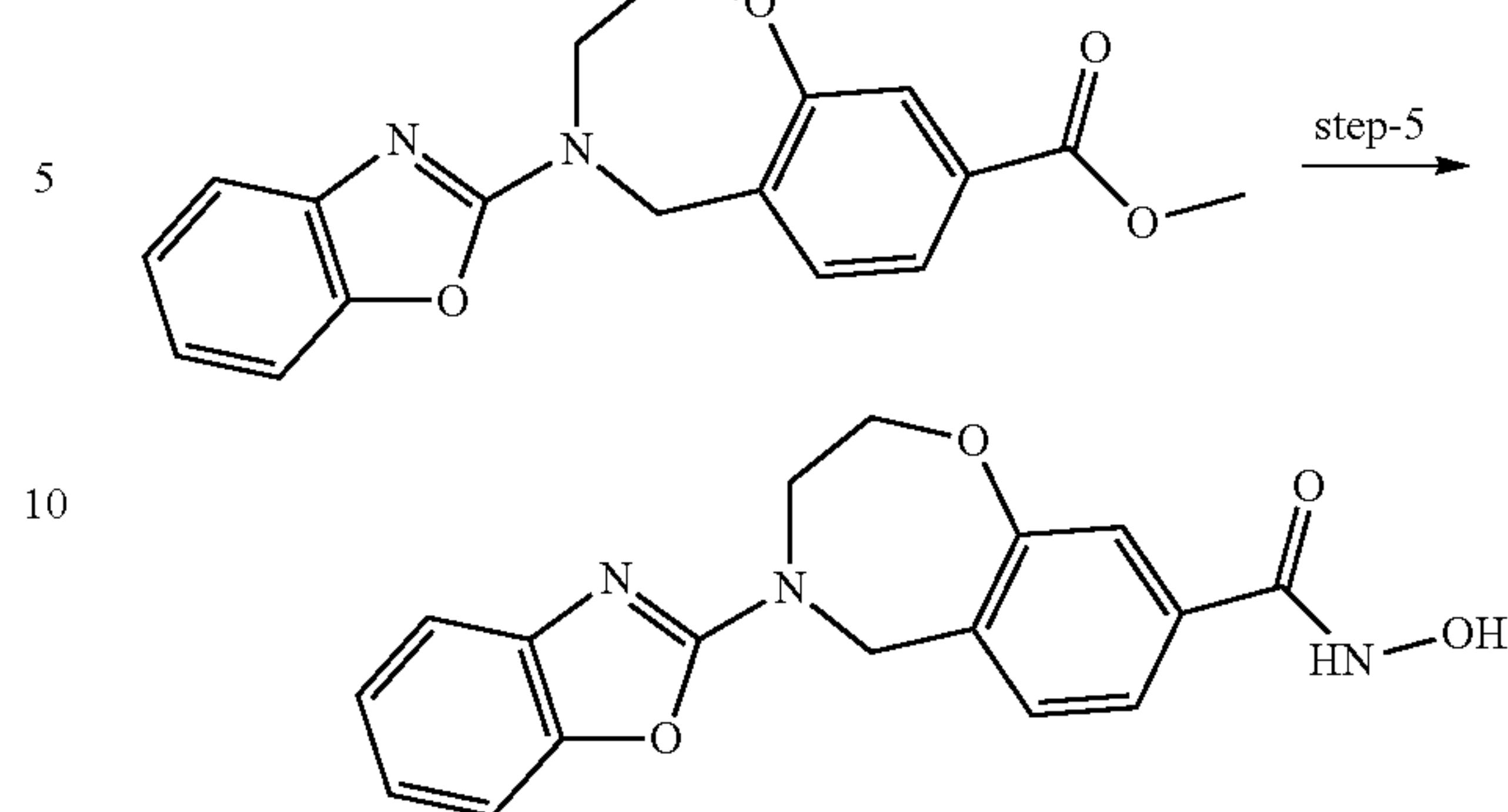
## Example 1

Preparation of 4-(benzo[d]oxazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

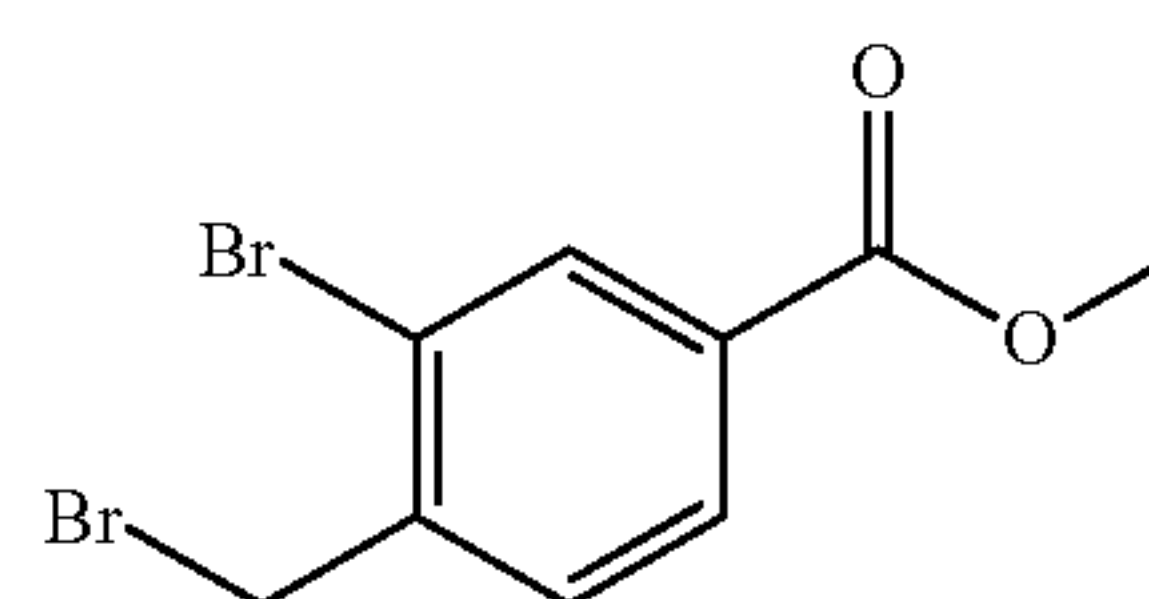


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-continued

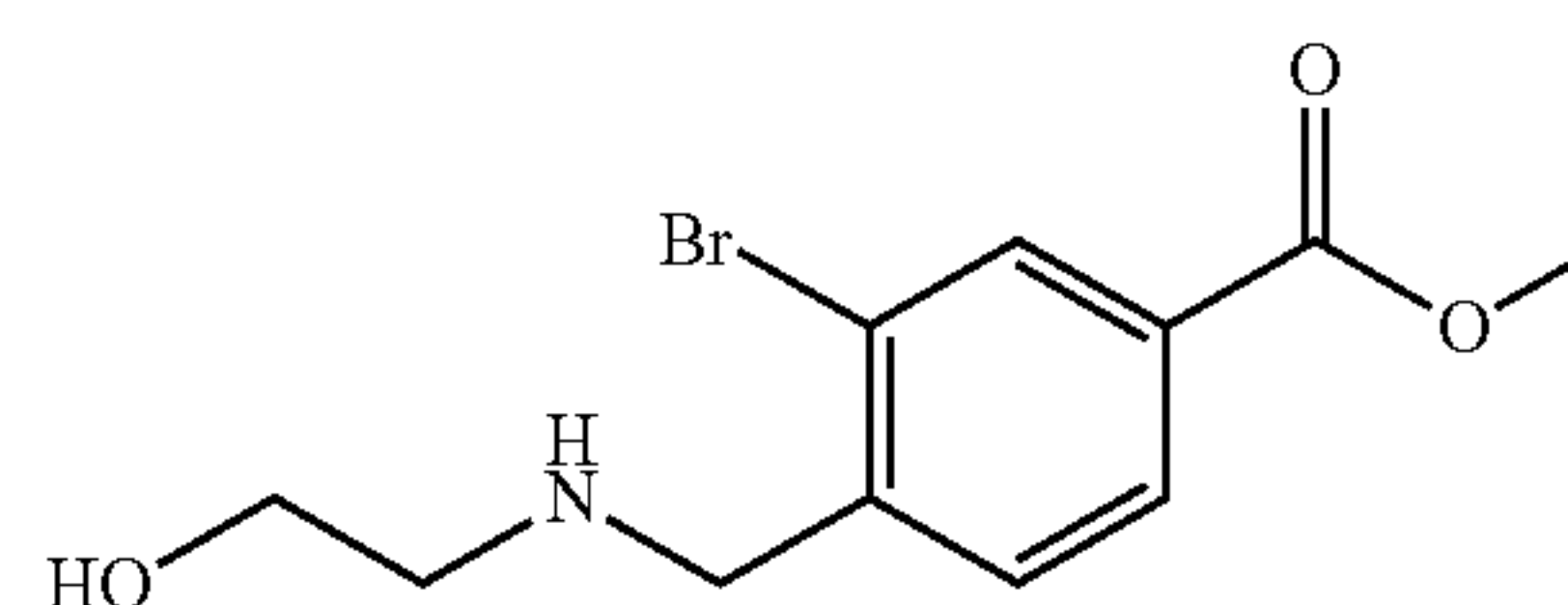


Step-1: Methyl 3-bromo-4-(bromomethyl)benzoate



Methyl 3-bromo-4-methylbenzoate (25 g, 109.14 mmol, 1 equiv), NBS (21.5 g, 120.80 mmol, 1.11 equiv), benzoyl peroxide (146 mg, 0.57 mmol, 0.01 equiv), and CCl<sub>4</sub> (120 mL) were placed in a 250-mL round-bottom flask. The resulting solution was stirred overnight at 85° C. in an oil bath. The resulting mixture was cooled and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:10) to afford the title compound as a white solid (20 g) and used without further purification.

Step-2: Methyl 3-bromo-4-((2-hydroxyethylamino)methyl)benzoate

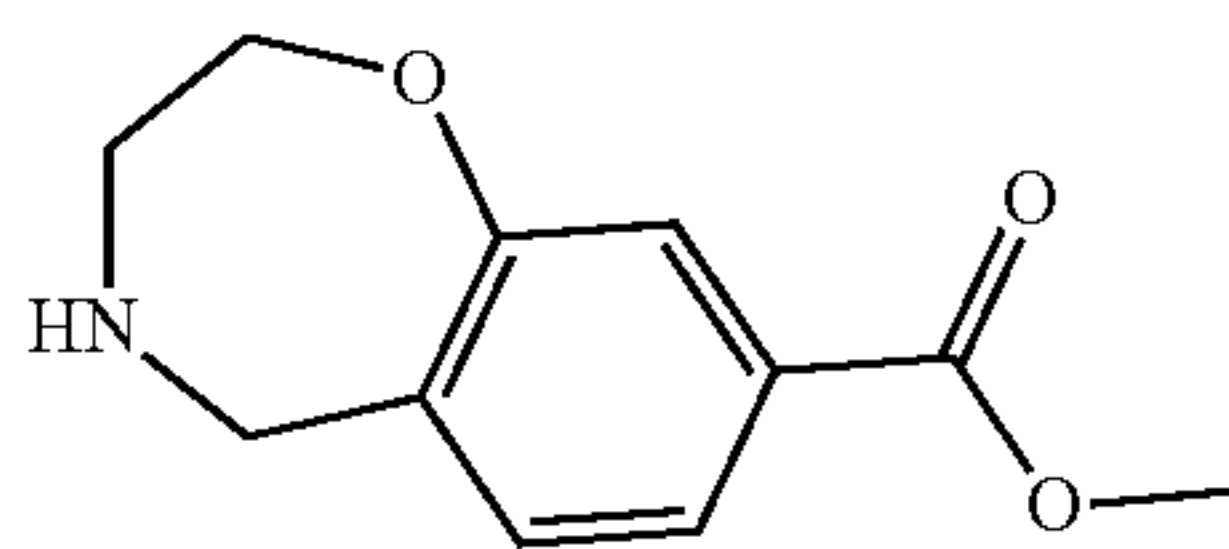


Methyl 3-bromo-4-(bromomethyl)benzoate (20 g, 64.94 mmol, 1 equiv), K<sub>2</sub>CO<sub>3</sub> (26.9 g, 194.63 mmol, 3 equiv), MeCN (100 mL), and 2-aminoethan-1-ol (4.76 g, 77.93 mmol, 1.20 equiv) were placed in a 250-mL round-bottom flask. The resulting solution was stirred for 2 h at -5° C. The resulting mixture was concentrated under vacuum, washed with water (50 mL) and EtOAc (50 mL). The organic layer was concentrated under vacuum and were placed in a 250-mL round-bottom flask. (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:20) to afford the title compound as a light yellow oil (16 g, 56% yield over 2 steps). MS: (ES, m/z): 288 [M+H]<sup>+</sup>.



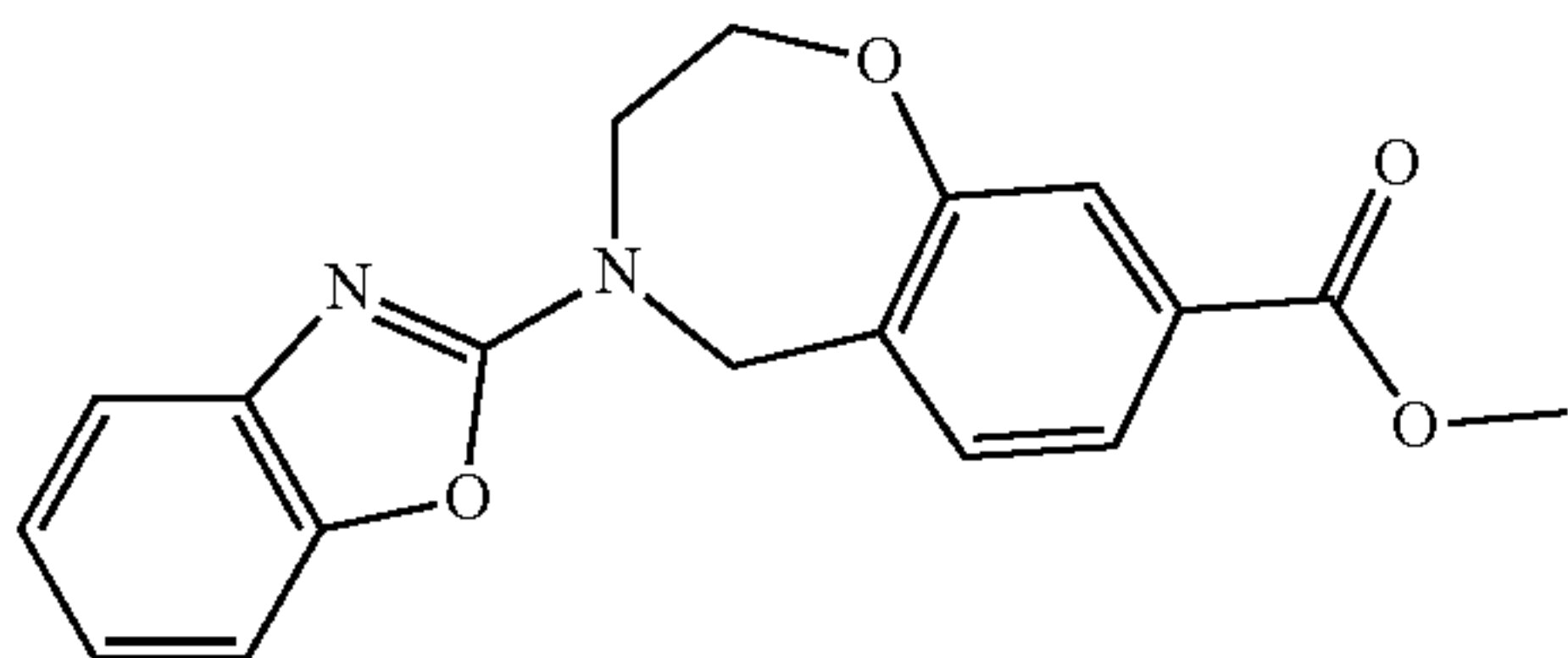
## 43

Step-3: Methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Methyl 3-bromo-4-((2-hydroxyethylamino)methyl)benzoate (7 g, 24.29 mmol, 1 equiv),  $K_2CO_3$  (6.6 g, 47.75 mmol, 1.97 equiv), CuI (912 mg, 4.79 mmol, 0.20 equiv), and isopropanol (100 mL) were placed in a 250-mL round-bottom flask. The resulting solution was stirred overnight at 110° C. in an oil bath. The solution was cooled and the solids were filtered out. The filtrate was concentrated under vacuum and purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a yellow oil (3 g, 60% yield).  $^1H$ -NMR (300 MHz,  $CDCl_3$ )  $\delta$ (ppm): 7.70-7.68 (t, 2H), 7.26-7.22 (t, 1H), 4.13-4.09 (t, 2H), 4.05 (s, 2H), 3.93 (s, 3H), 3.50 (s, 1H), 3.30-3.28 (t, 2H). MS: (ES, m/z): 208  $[M+H]^+$ .

Step-4: Methyl 4-(benzo[d]oxazol-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

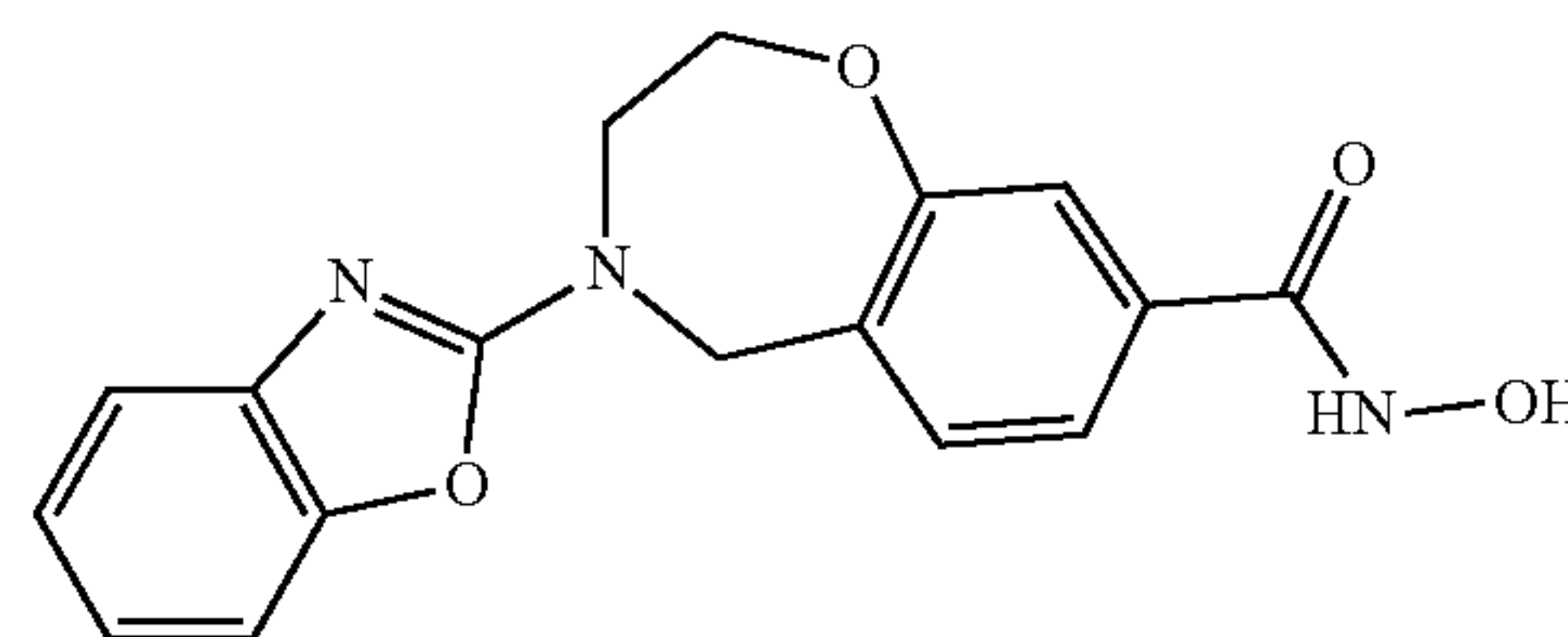


Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed methyl

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2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (200 mg, 0.97 mmol, 1 equiv), 2-bromo-1H-1,3-benzoxazole (285 mg, 1.45 mmol, 1.5 equiv), CuI (37 mg, 0.19 mmol, 0.2 equiv), ethane-1,2-diol (0.1 mL) and phosphoroxol potassium (263 mg, 1.95 mmol, 2 equiv). The resulting solution was stirred overnight at 110° C. in an oil bath. The resulting mixture was cooled and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:5) to afford the title compound as a yellow oil (197 mg, 63% yield). MS: (ES, m/z): 325  $[M+H]^+$ .

Step-5: 4-(Benzo[d]oxazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



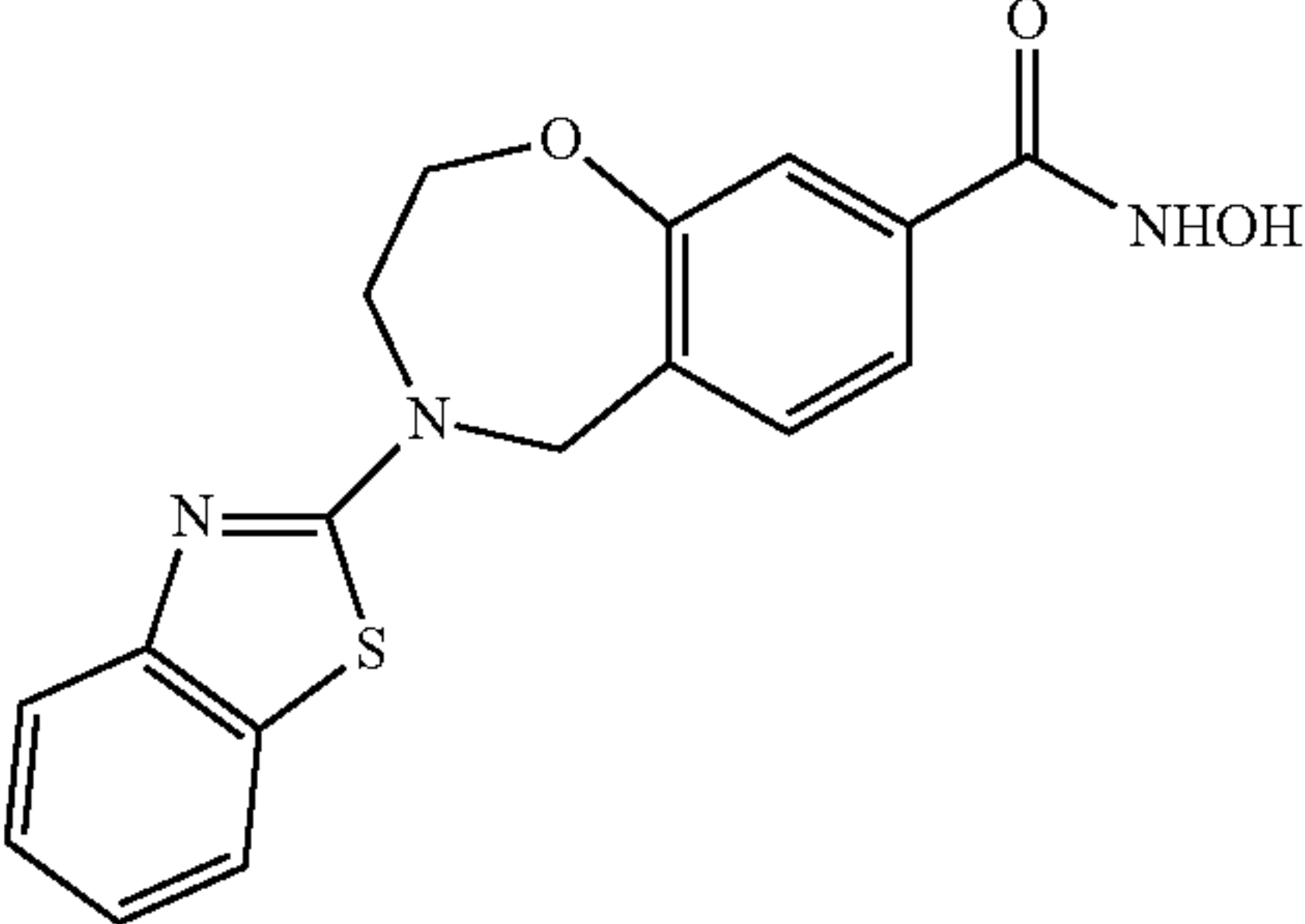
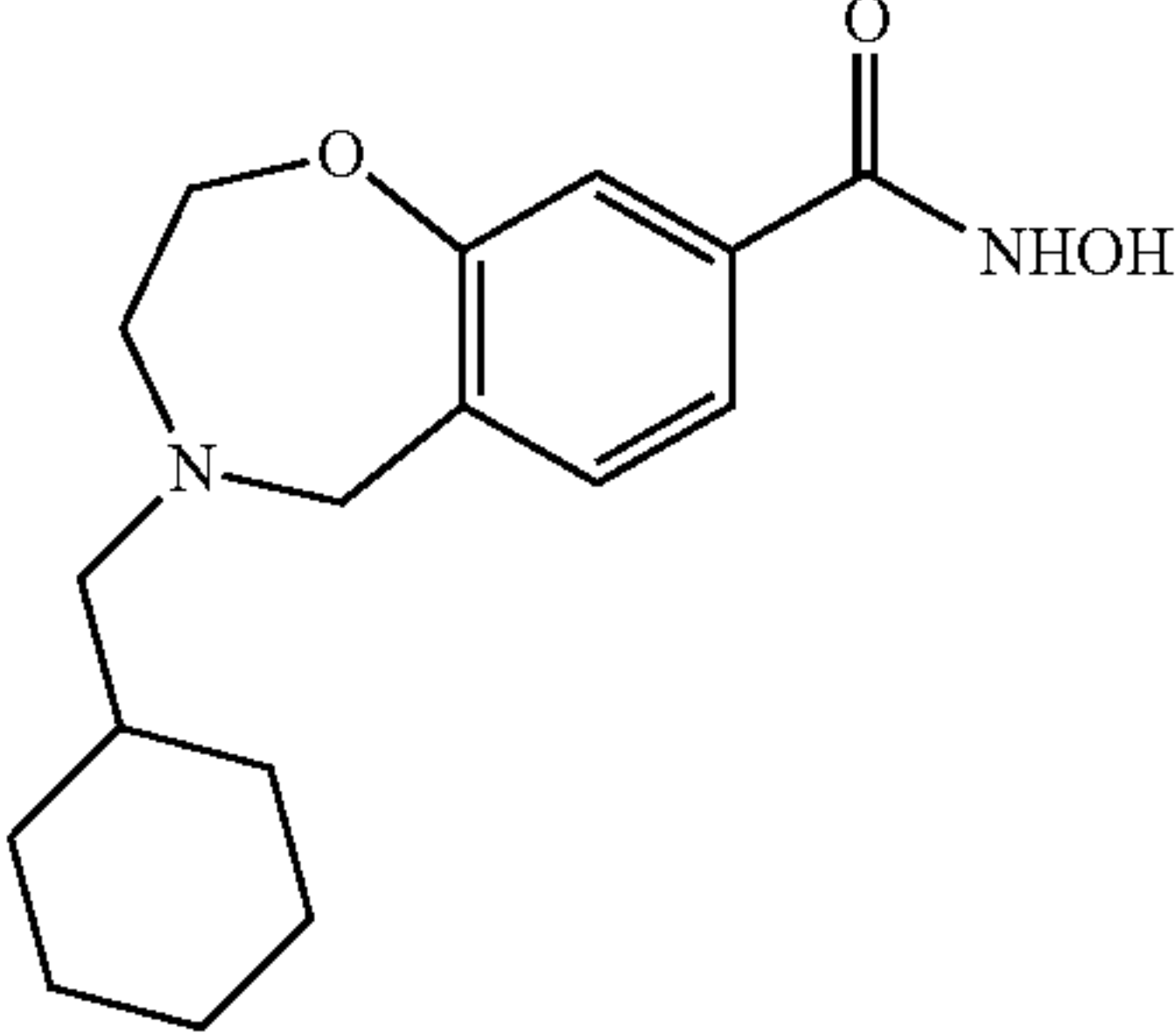
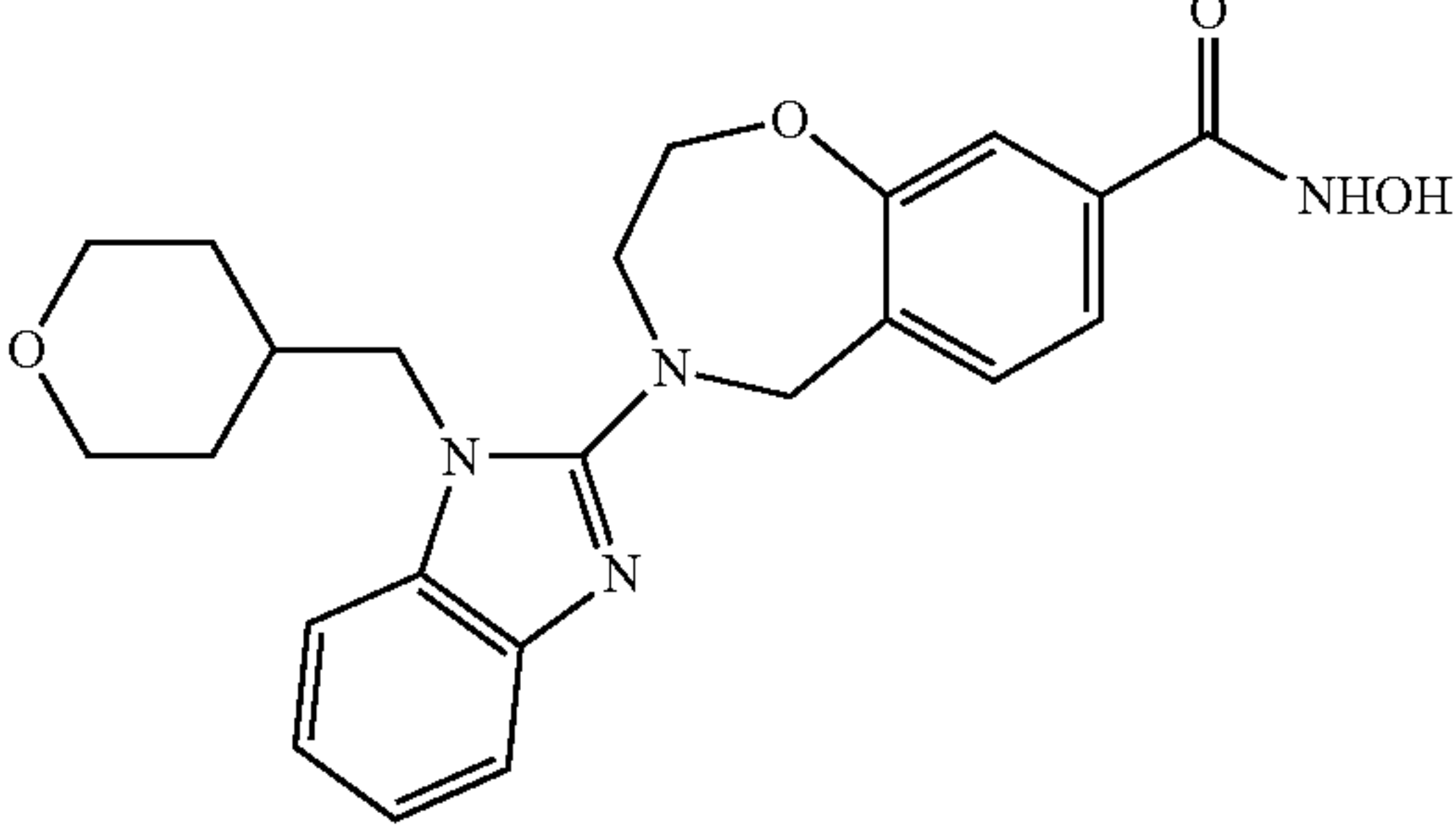
Into a 100-mL round-bottom flask, was placed methyl 4-(benzo[d]oxazol-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.31 mmol, 1 equiv),  $NH_2OH$  (50% in water, 1 mL), aq. 1N NaOH (0.62 mL, 2 equiv), and THF (3 mL). The resulting solution was stirred overnight at 40° C. in an oil bath. The crude product (80 mg) was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5  $\mu m$ , 19x150 mm; Mobile Phase A: Water/0.05% Formic Acid; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 5% B to 50% B in 9 min; Detector: UV 254, 220 nm) to afford the title compound as a pink solid (29 mg, 29% yield).  $^1H$ -NMR (400 MHz,  $DMSO-d_6$ )  $\delta$ (ppm): 11.16 (s, 1H), 9.03 (s, 1H), 7.50-6.98 (t, 7H), 4.84 (s, 2H), 4.26-4.24 (t, 2H), 4.08-4.06 (t, 2H). MS: (ES, m/z): 326  $[M+H]^+$ .

TABLE 1

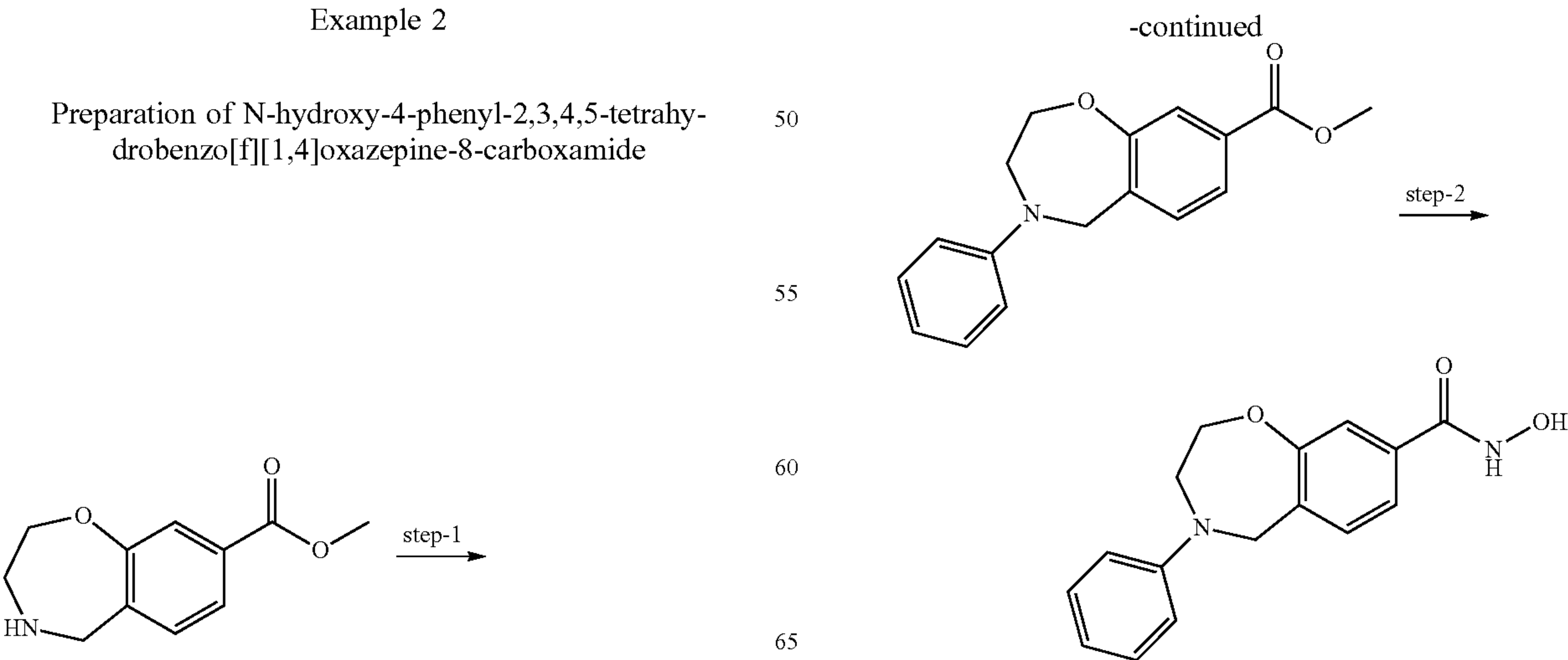
The following compounds were prepared according to the method of Example 1.		
Structure	Found M + H	$^1H$ -NMR (300 MHz, $DMSO-d_6$ ) $\delta$ (ppm)
	(ES, m/z): 421 $[M + H]^+$	11.18 (s, 1H), 9.06 (s, 1H), 7.50-7.34 (m, 5H), 7.06-7.03 (m, 2H), 4.55-4.47 (t, 1H), 4.35 (s, 1H), 4.02 (d, 1H), 3.73 (s, 1H), 1.79 (s, 1H), 1.16-1.47 (m, 3H), 1.23-1.10 (m, 2H), 0.98-0.78 (m, 5H)



TABLE 1-continued

The following compounds were prepared according to the method of Example 1.		
Structure	Found M + H	<sup>1</sup> H-NMR (300 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 342 [M + H] <sup>+</sup>	10.98 (s, 1H), 9.04 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.52-7.22 (m, 5H), 7.08-7.02 (m, 1H), 4.83 (s, 2H), 4.27-4.11 (m, 4H)
	(ES, m/z): 305 [M + H] <sup>+</sup>	11.16 (s, 1H), 9.03 (s, 1H), 8.18 (s, 1H), 7.39-7.20 (m, 3H), 3.99 (s, 2H), 3.75-3.73 (d, J = 8 Hz, 2H), 2.96 (s, 2H), 2.20-2.18 (d, J = 5.6 Hz, 2H), 1.70-1.63 (m, 4H), 1.47-1.46 (d, J = 8 Hz, 1H), 1.24-1.11 (m, 4H), 0.85-0.77 (m, 2H)
	(ES, m/z): 423 [M + H] <sup>+</sup>	11.25 (s, 1H), 9.06 (br s, 1H), 7.70-7.72 (m, 1H), 7.24-7.51 (m, 6H), 4.88 (s, 2H), 4.50 (s, 2H), 4.08-4.10 (d, J = 7.2 Hz, 2H), 3.91 (s, 2H), 3.53-3.59 (d, J = 24.4 Hz, 2H), 2.87-2.94 (m, 2H), 1.80-1.91 (m, 1H), 0.92 (s, 4H)

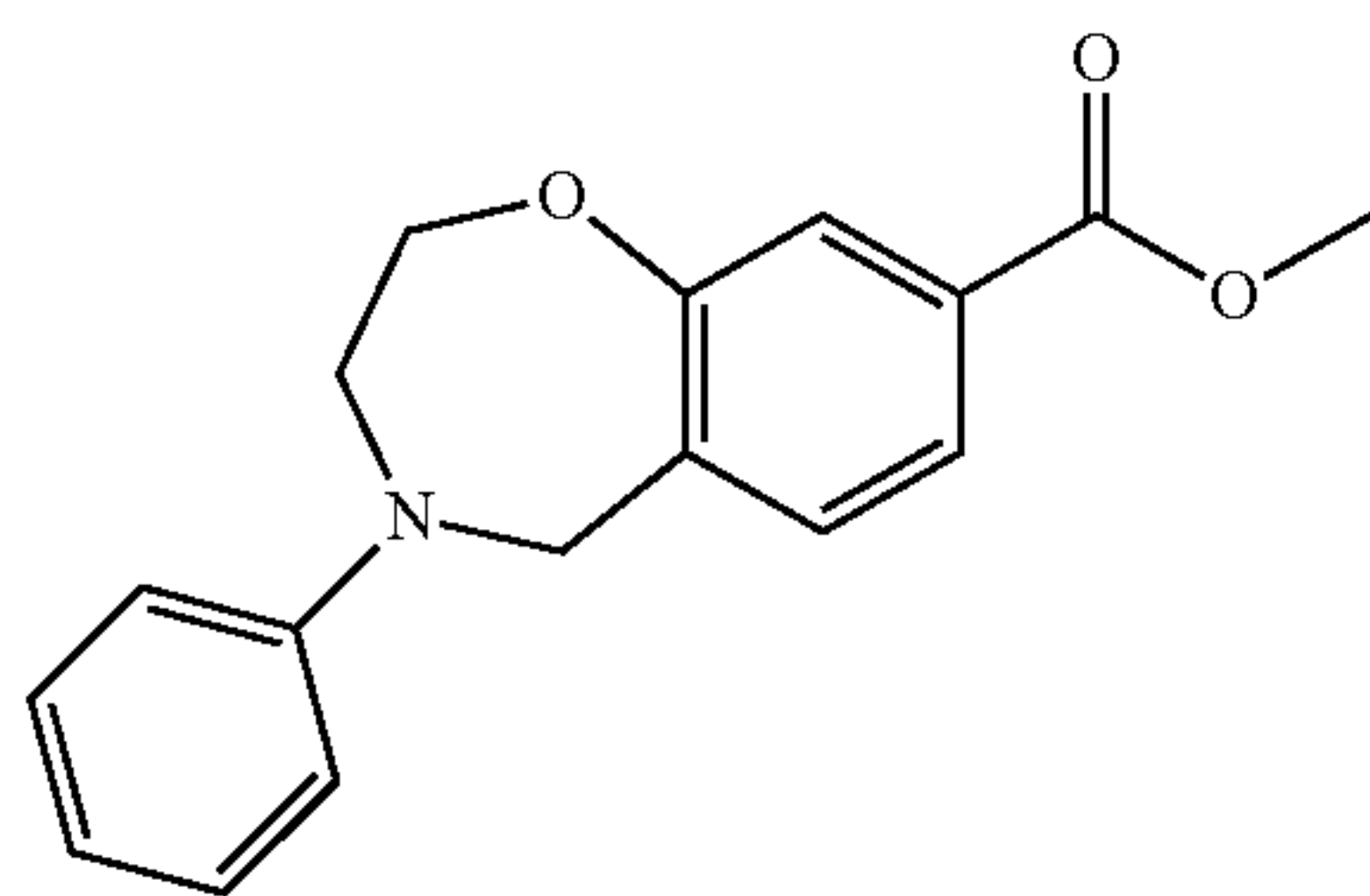
Example 2





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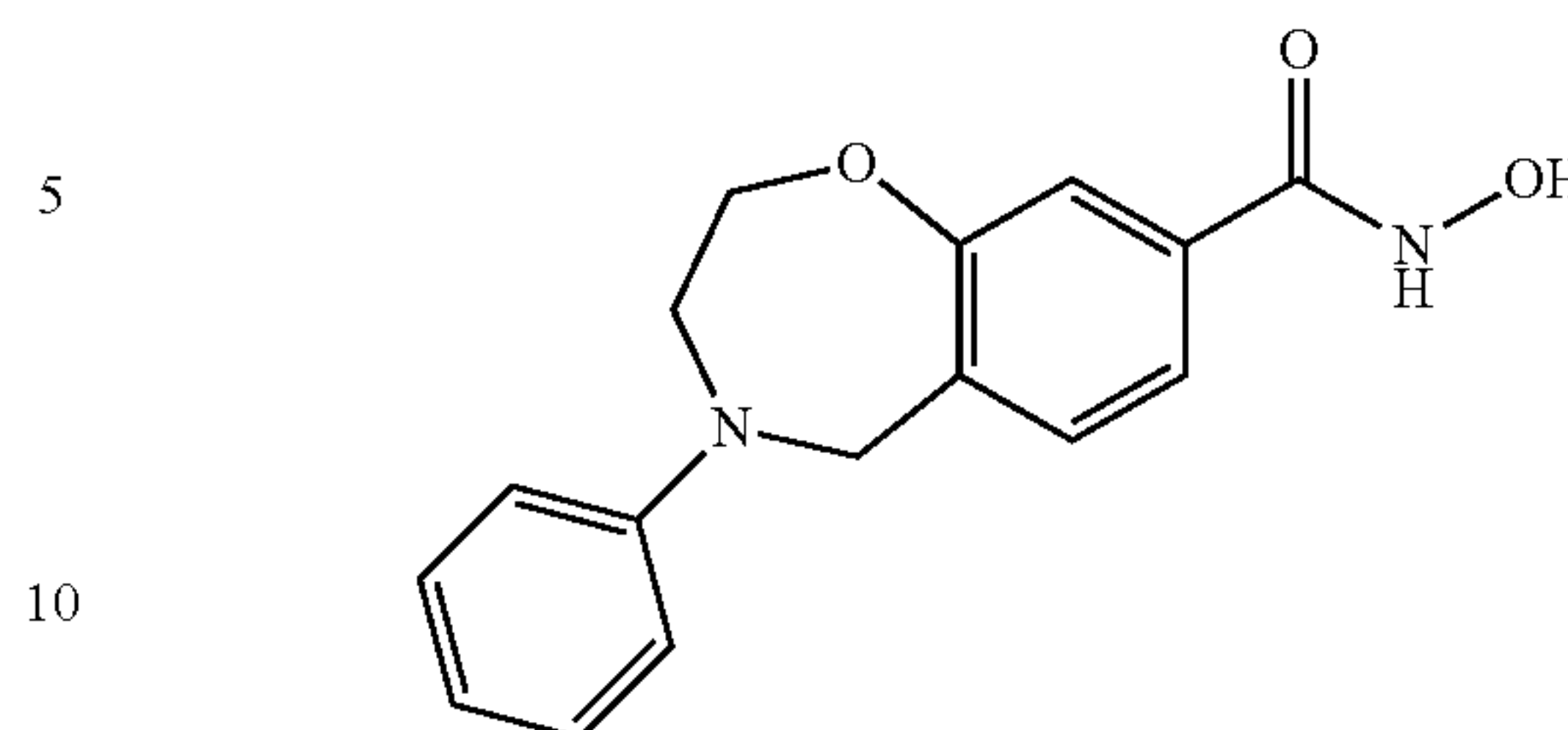
Step-1: Methyl 4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 50-mL round-bottom flask, was placed methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.48 mmol, 1 equiv), Pd<sub>2</sub>(dba)<sub>3</sub> (50 mg, 0.05 mmol, 0.11 equiv), Xantphos (14 mg, 0.02 mmol, 0.05 equiv), Cs<sub>2</sub>CO<sub>3</sub> (326 mg, 1 mmol, 2.08 equiv), dioxane (10 mL) and bromobenzene (117 mg, 0.75 mmol, 1.54 equiv). The resulting mixture was stirred overnight at 100° C. in an oil bath. After cooling, the solids were filtered out and the filtrate was concentrated under vacuum. The residue was purified by prep-TLC (EtOAc/pet. ether, 1:5) to afford the title compound as a light yellow oil (50 mg, 37% yield). MS: (ES, m/z): 284 [M+H]<sup>+</sup>.

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Step-2: N-Hydroxy-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 100-mL round-bottom flask, was placed methyl 4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (50 mg, 0.18 mmol, 1 equiv), NH<sub>2</sub>OH (50% in water, 1 mL, 50 equiv), aq. 1N NaOH (0.36 mL, 2 equiv) and THF (3 mL). The resulting solution was stirred overnight at 40° C. in an oil bath. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 ODB, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% Formic Acid; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 5% B to 55% B in 8 min; Detector: UV 254, 220 nm) to afford the title compound as a pink oil (2.5 mg, 5% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.12 (s, 1H), 9.03 (s, 1H), 7.56-6.56 (m, 8H), 4.66 (s, 2H), 4.17-4.10 (t, 2H), 3.91-3.80 (t, 2H). MS: (ES, m/z): 326 [M+H]<sup>+</sup>.

TABLE 2

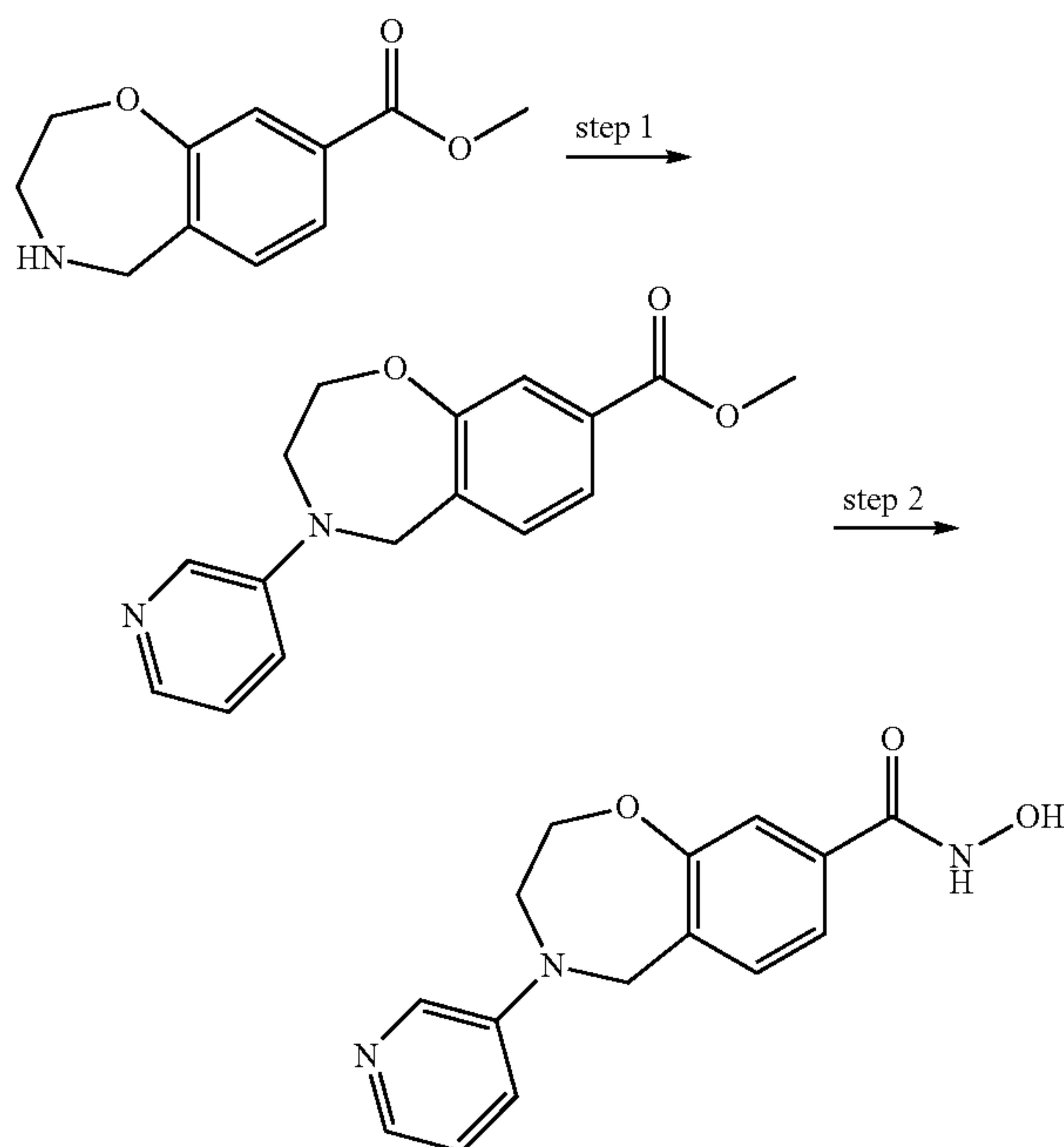
The following compounds were prepared according to the method of Example 2.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 11.15 (s, 1H), 9.02 (s, 1H), 7.79-7.76 (t, 378 1H), 7.60-7.58 (t, 1H), 7.41-7.39 (t, 1H), [M + H] <sup>+</sup> 7.30-7.22 (t, 3H), 4.86 (s, 2H), 4.20-4.19 (t, 2H), 4.06-4.05 (t, 2H)	
	(ES, m/z): 11.11 (s, 1H), 9.04 (s, 1H), 7.59-7.57 (t, 353 1H), 7.50-7.43 (t, 1H), 7.30-7.28 (t, 2H), [M + H] <sup>+</sup> 7.09-7.08 (t, 1H), 6.90-6.87 (t, 1H), 4.69 (s, 2H), 4.13-4.11 (t, 2H), 3.90-3.88 (t, 2H)	
	(ES, m/z): 11.06 (s, 1H), 9.03 (s, 1H), 8.04-8.05 (t, 286 J = 1.5 Hz, 1H), 7.29-7.49 (m, 4H), [M + H] <sup>+</sup> 6.86-6.89 (d, J = 8.7 Hz, 1H), 6.53-6.57 (m, 1H), 4.77 (s, 2H), 4.10 (s, 4H)	



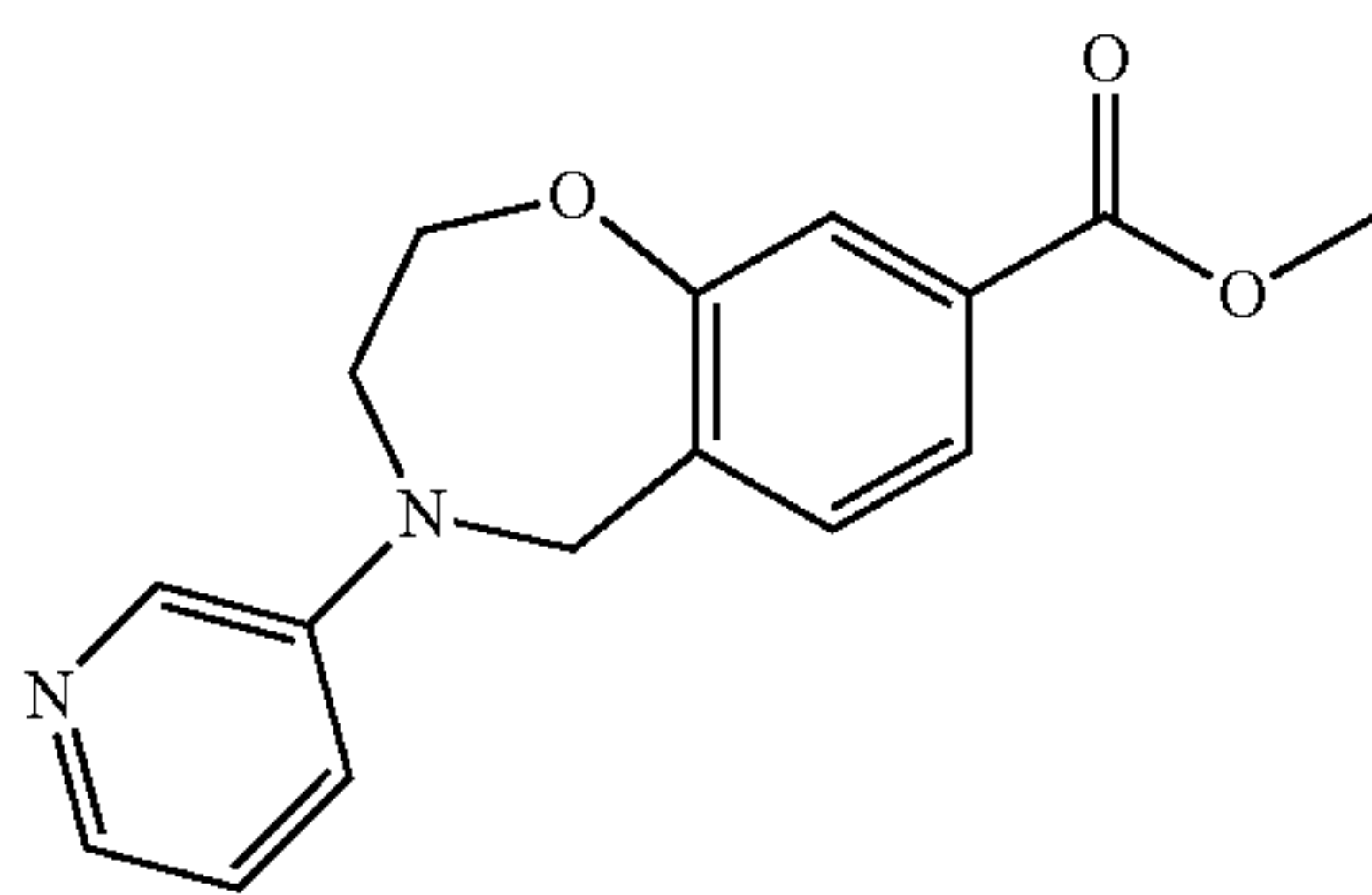
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## Example 3

Preparation of N-hydroxy-4-(pyridin-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



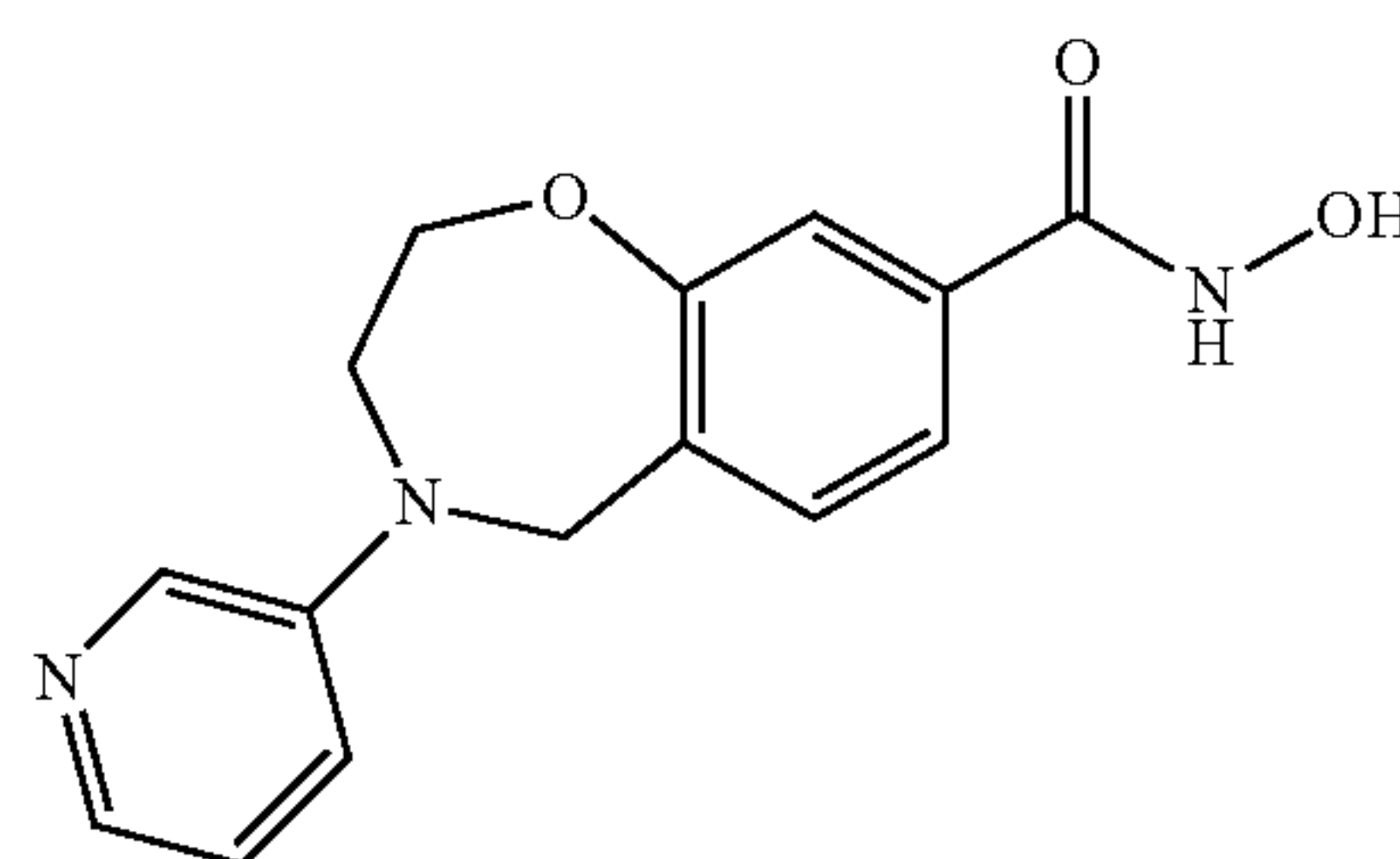
Step-1: Methyl 4-(pyridin-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



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Into a 25-mL sealed tube, was placed a solution of methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (200 mg, 0.97 mmol, 1 equiv) in 1,4-dioxane (10 mL), 3-bromopyridine (171 mg, 1.08 mmol, 1.5 equiv), Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (15 mg, 0.02 equiv), BINAP (20 mg, 0.03 mmol, 0.03 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (489 mg, 1.50 mmol, 2 equiv). The resulting mixture was stirred for 1.5 h at 150° C. in a microwave reactor. The reaction mixture was concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (30 mL) and then extracted with EtOAc (3×100 mL). The organic layer was concentrated and the residue was purified by silica gel chromatography (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:10) to afford the title compound as a light yellow oil (50 mg, 18% yield). MS: (ES, m/z): 285 [M+H]<sup>+</sup>.

Step-2: N-Hydroxy-4-(pyridin-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 100-mL round-bottom flask, was placed a solution of methyl 4-(pyridin-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (50 mg, 0.18 mmol, 1 equiv) in THF/MeOH (4:1, 2.5 mL), NH<sub>2</sub>OH (50% in water, 1 mL, 60 equiv), aq. 1N NaOH (0.5 mL, 2 equiv). The resulting solution was stirred overnight at room temperature. The mixture was purified by Prep-HPLC (Column: HSS C18 OBD, 1.8 μm, 2.1×50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2 min, hold 0.6 min; Detector: UV 254 nm) to afford the title compound as a yellow solid (3.3 mg, 6% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 8.33 (b, 1H), 8.26 (s, 1H), 7.83 (b, 1H), 7.62 (s, 1H), 7.39-7.09 (m, 4H), 4.72 (s, 1H), 4.13 (b, 2H), 3.93 (s, 2H). MS: (ES, m/z): 286 [M+H]<sup>+</sup>.

TABLE 3

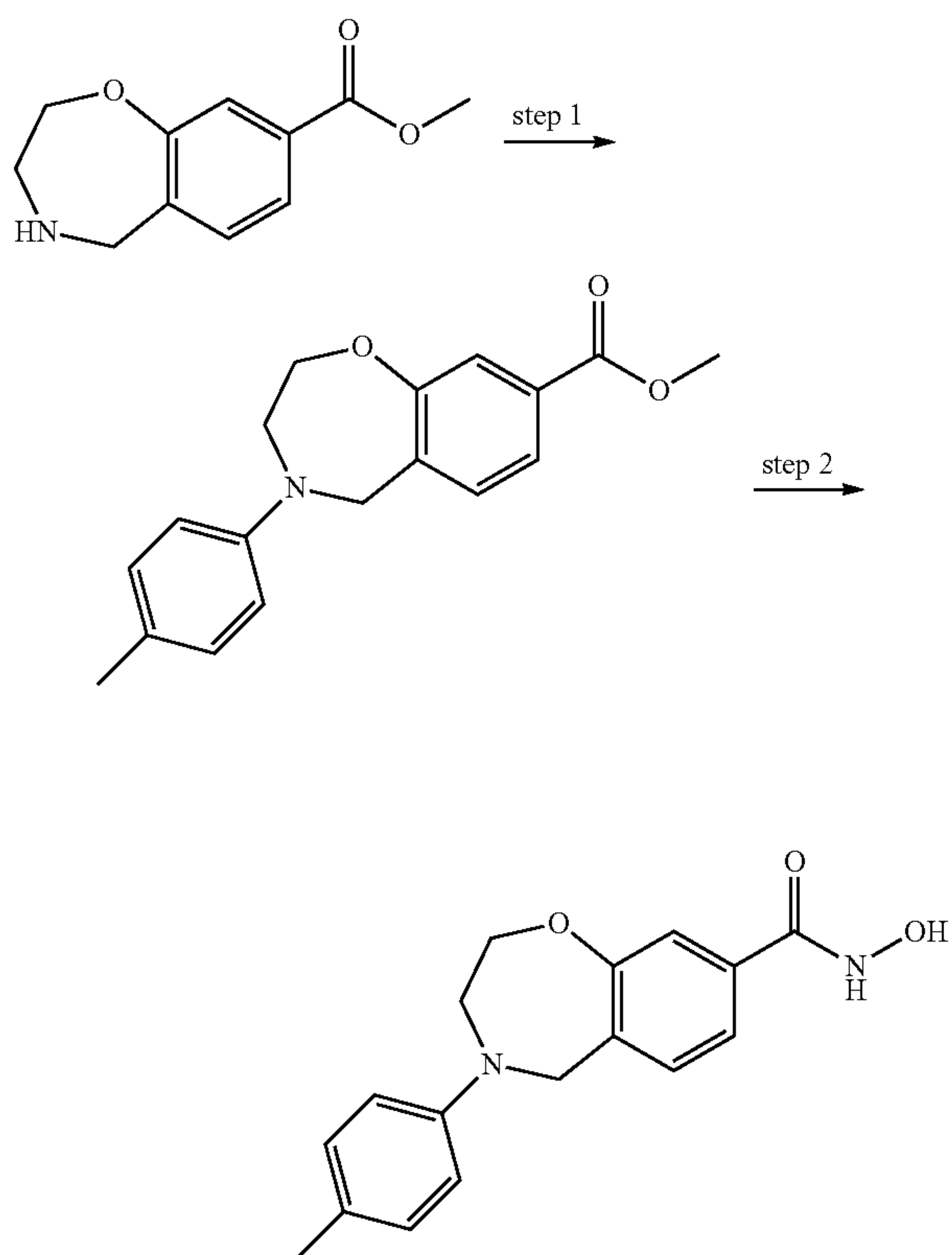
The following compound was prepared according to the method of Example 3.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 286 [M + H] <sup>+</sup>	8.30-8.08 (m, 3H), 7.58-7.30 (m, 3H), 6.81 (s, 2H), 4.70 (s, 2H), 4.13 (s, 2H), 3.92 (s, 2H)



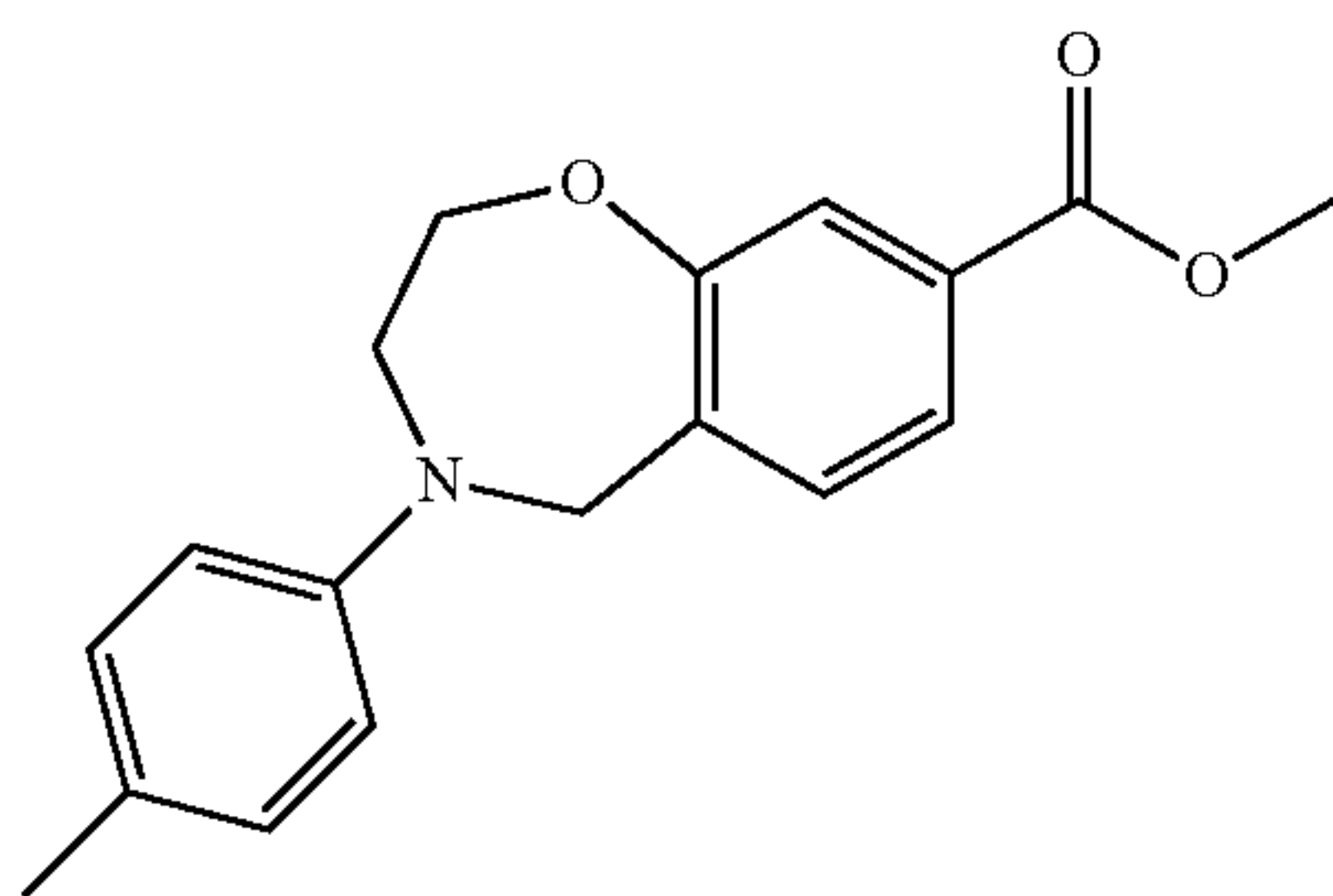
**51**

## Example 4

Preparation of N-hydroxy-4-(p-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



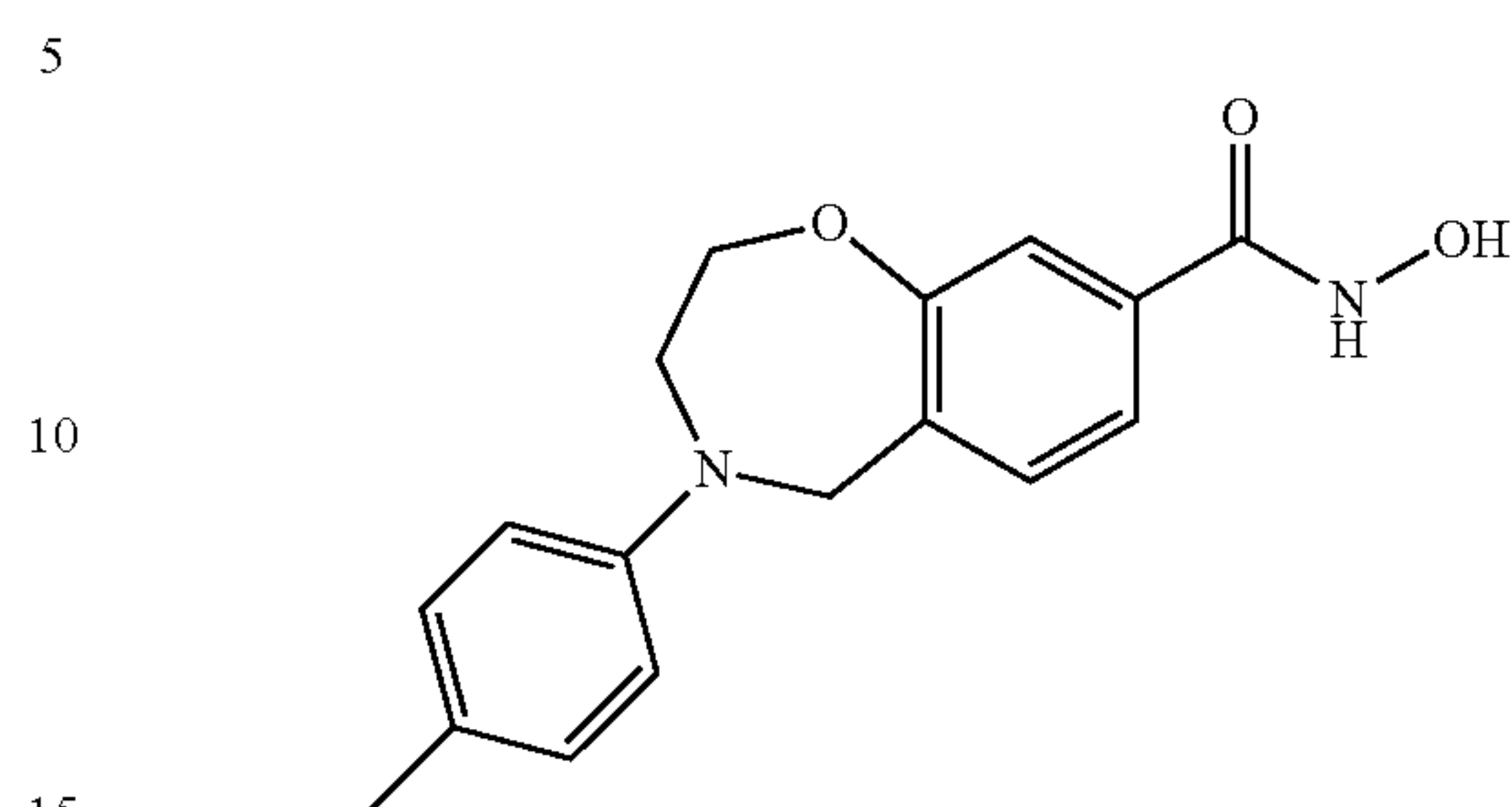
Step-1: Methyl 4-(p-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 100-mL round-bottom flask, was placed methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (200 mg, 0.97 mmol, 1 equiv), p-tolylboronic acid (162 mg, 1.19 mmol, 1.24 equiv), Cu(OAc)<sub>2</sub> (18 mg, 0.10 mmol, 0.1 equiv), pyridine (16 mg, 0.20 mmol, 0.21 equiv), CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The resulting solution was stirred for 2 h at room temperature, then concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:5) to afford the title compound as a light yellow solid (120 mg, 42% yield). MS: (ES, m/z): 298 [M+H]<sup>+</sup>.

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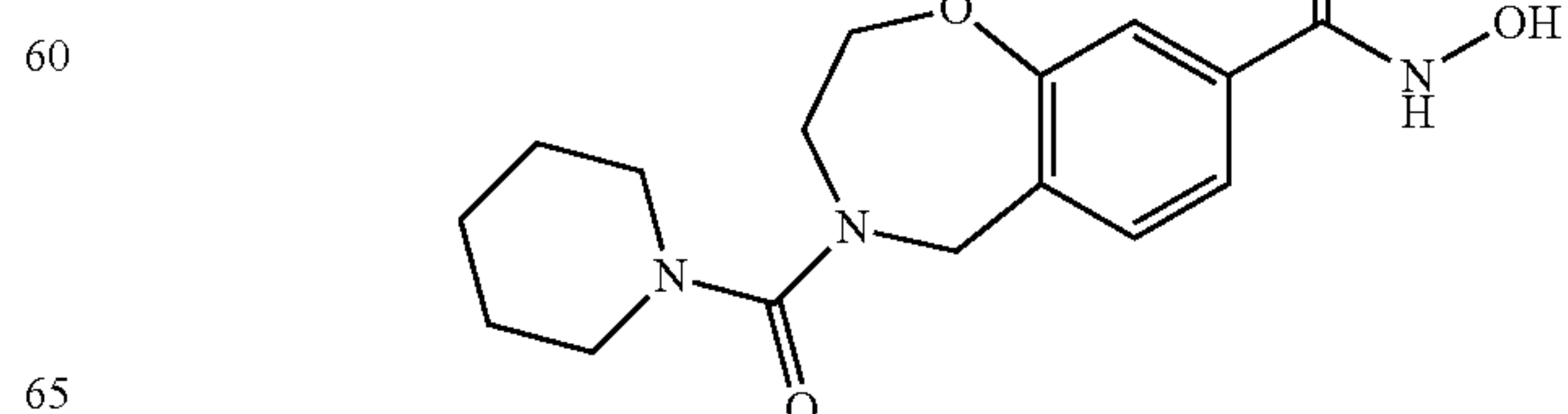
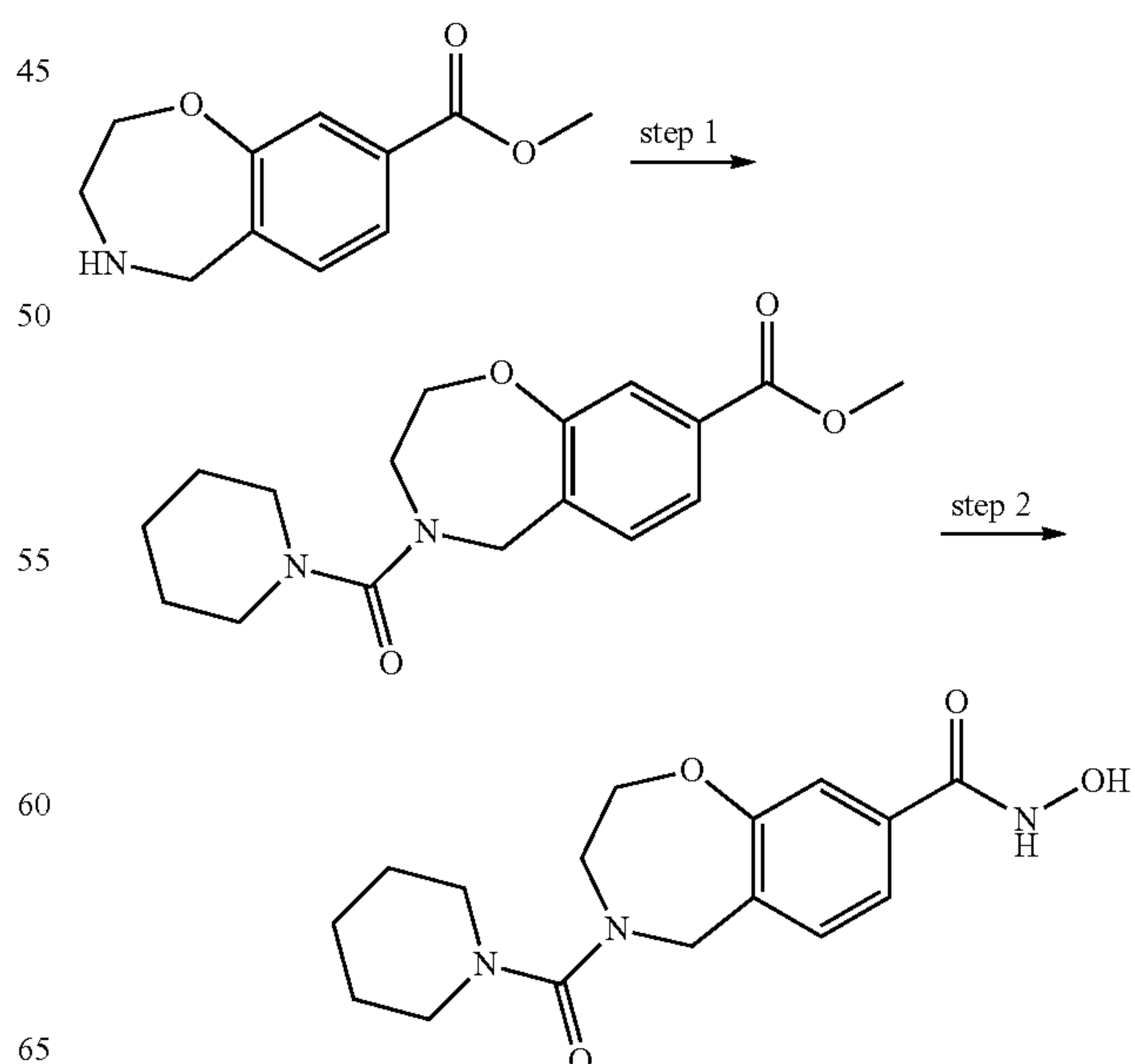
Step-2: N-Hydroxy-4-(p-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 100-mL round-bottom flask was placed methyl 4-(p-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (120 mg, 0.40 mmol, 1 equiv), NH<sub>2</sub>OH (50% in water, 1 mL, 38 equiv), aq. 1N NaOH (1 mL, 2.5 equiv), and THF/MeOH (4:1, 3 mL). The resulting solution was stirred overnight at 40° C. in an oil bath. The mixture was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% Formic Acid; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 5% B to 60% B in 10 min; Detector: UV 254, 220 nm) to afford the title compound as a pink solid (31 mg, 26% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.11 (s, 1H), 9 (s, 1H), 7.55-7.52 (t, 1H), 7.37-7.34 (t, 1H), 7.27-7.27 (t, 1H), 6.93-6.90 (t, 2H), 6.78-6.79 (t, 2H), 4.62 (s, 2H), 4.11-4.09 (t, 2H), 3.85-3.83 (t, 2H), 2.11 (s, 3H). MS: (ES, m/z): 299 [M+H]<sup>+</sup>.

## Example 5

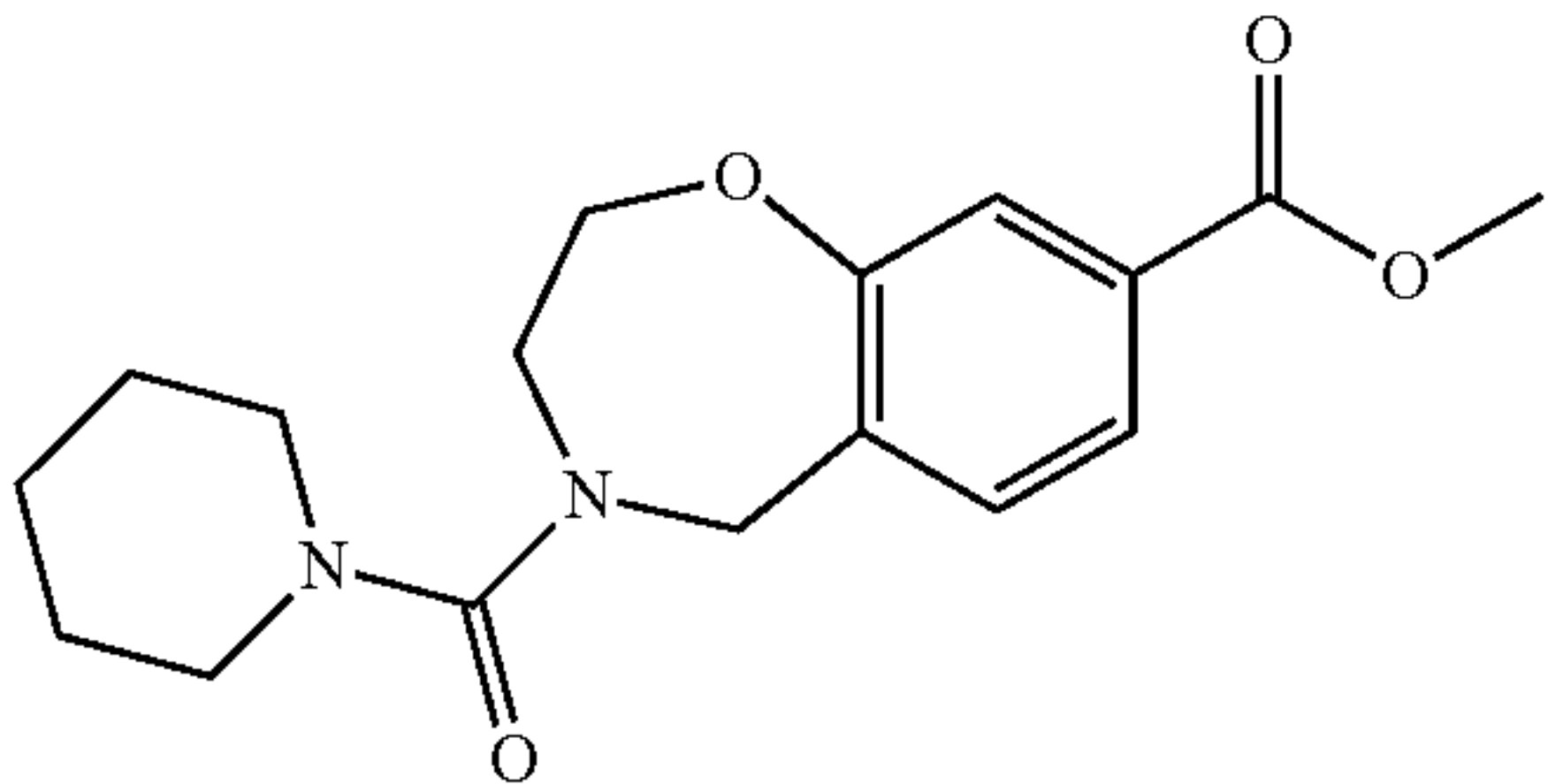
Preparation of N-hydroxy-4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide





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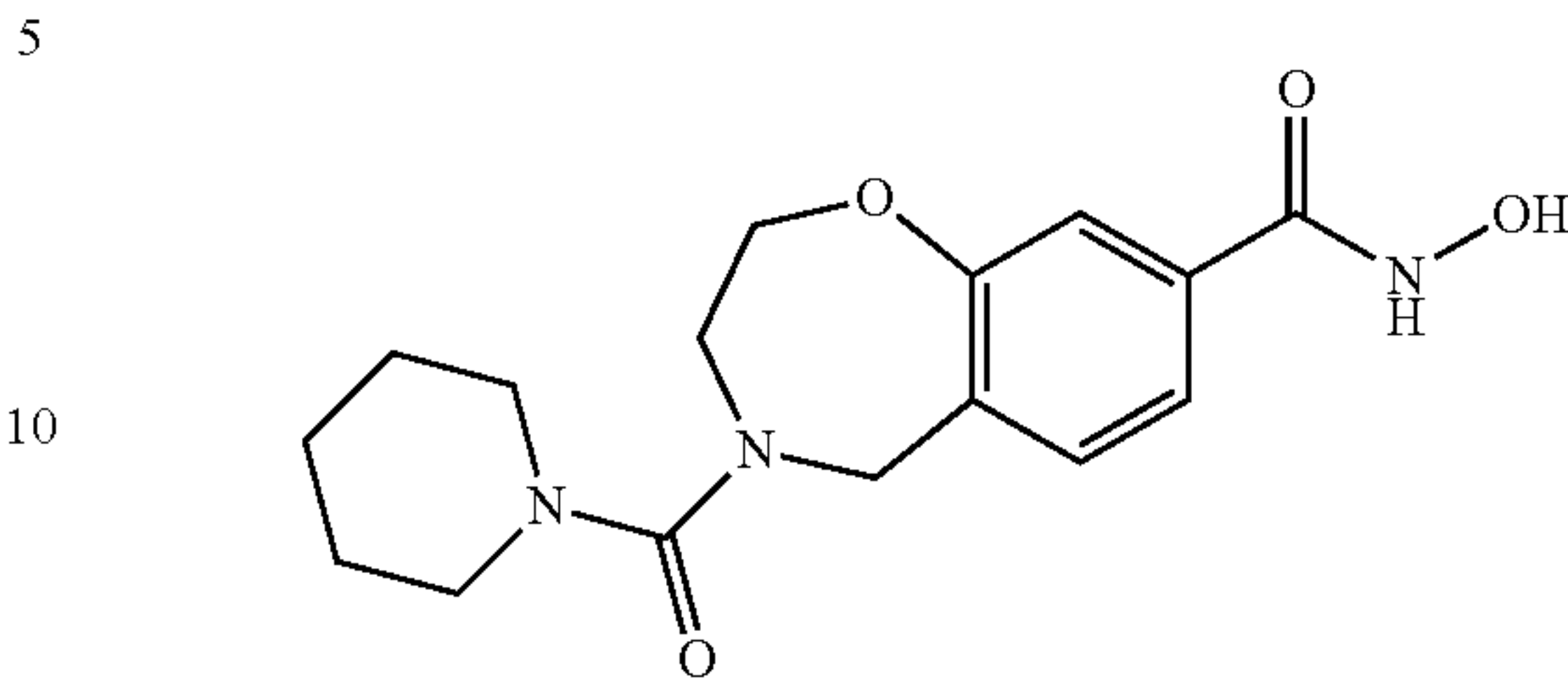
Step-1: Methyl 4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 10-mL round-bottom flask, was placed a solution of methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (104 mg, 0.50 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), Et<sub>3</sub>N (101.5 mg, 1 mmol, 2 equiv) and piperidine-1-carbonyl chloride (82 mg, 0.56 mmol, 1.1 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of water (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a white solid (133 mg, 83% yield). MS: (ES, m/z): 319 [M+H]<sup>+</sup>.

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Step-2: N-Hydroxy-4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 25-mL round-bottom flask, was placed a solution of methyl 4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (133 mg, 0.42 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), aq. 1N NaOH (0.836 mL, 2 equiv) and NH<sub>2</sub>OH (50% in water, 828 mg, 25 mmol, 30 equiv). The resulting solution was stirred for 2 h at room temperature. The pH value of the solution was adjusted to 6 with 2N HCl. The crude product was purified by Prep-HPLC (Column: HSS C18 OBD, 1.8 μm, 2.1×50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2 min, hold 0.6 min; Detector: UV 254, 220 nm) to afford the title compound as a pink solid (49 mg, 27% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.18 (s, 1H), 7.36-7.39 (m, 1H), 7.28-7.31 (t, J=1.6 Hz, 2H), 4.37 (s, 2H), 4.17-4.20 (t, J=4.4 Hz, 2H), 3.55-3.57 (t, J=4.8 Hz, 2H), 3.06-3.07 (d, J=5.2 Hz, 2H), 1.49-1.51 (d, J=6 Hz, 6H). MS: (ES, m/z): 320 [M+H]<sup>+</sup>.

TABLE 4

The following compounds were prepared according to the method of Example 5.		
Structure	Found	
	M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 359 [M + H] <sup>+</sup>	11.20 (s, 1H), 7.30-7.46 (m, 3H), 6.99-7.01 (d, J = 8.8 Hz, 1H), 6.87-6.89 (t, J = 2.4 Hz, 3H), 4.72 (s, 1H), 4.61 (s, 1H), 4.25 (s, 1H), 4.16 (s, 1H), 3.98 (s, 1H), 3.83 (s, 1H), 3.72 (s, 3H)
	(ES, m/z): 335 [M + H] <sup>+</sup>	11.17 (s, 1H), 7.40-7.42 (d, J = 7.2 Hz, 1H), 7.28-7.33 (t, J = 8 Hz, 2H), 4.51 (s, 3H), 4.07 (s, 2H), 3.76 (s, 2H), 1.59-1.67 (m, 4H), 1.28-281.42 (m, 6H)

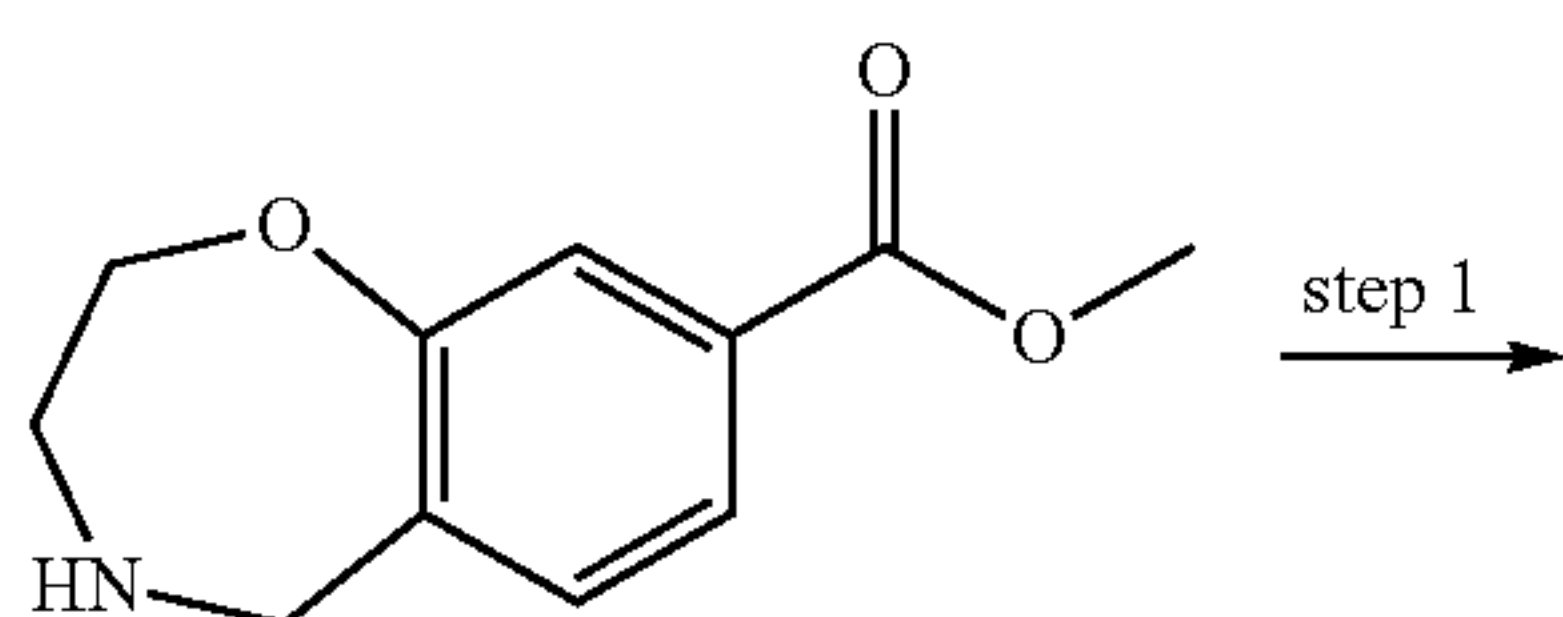


TABLE 4-continued

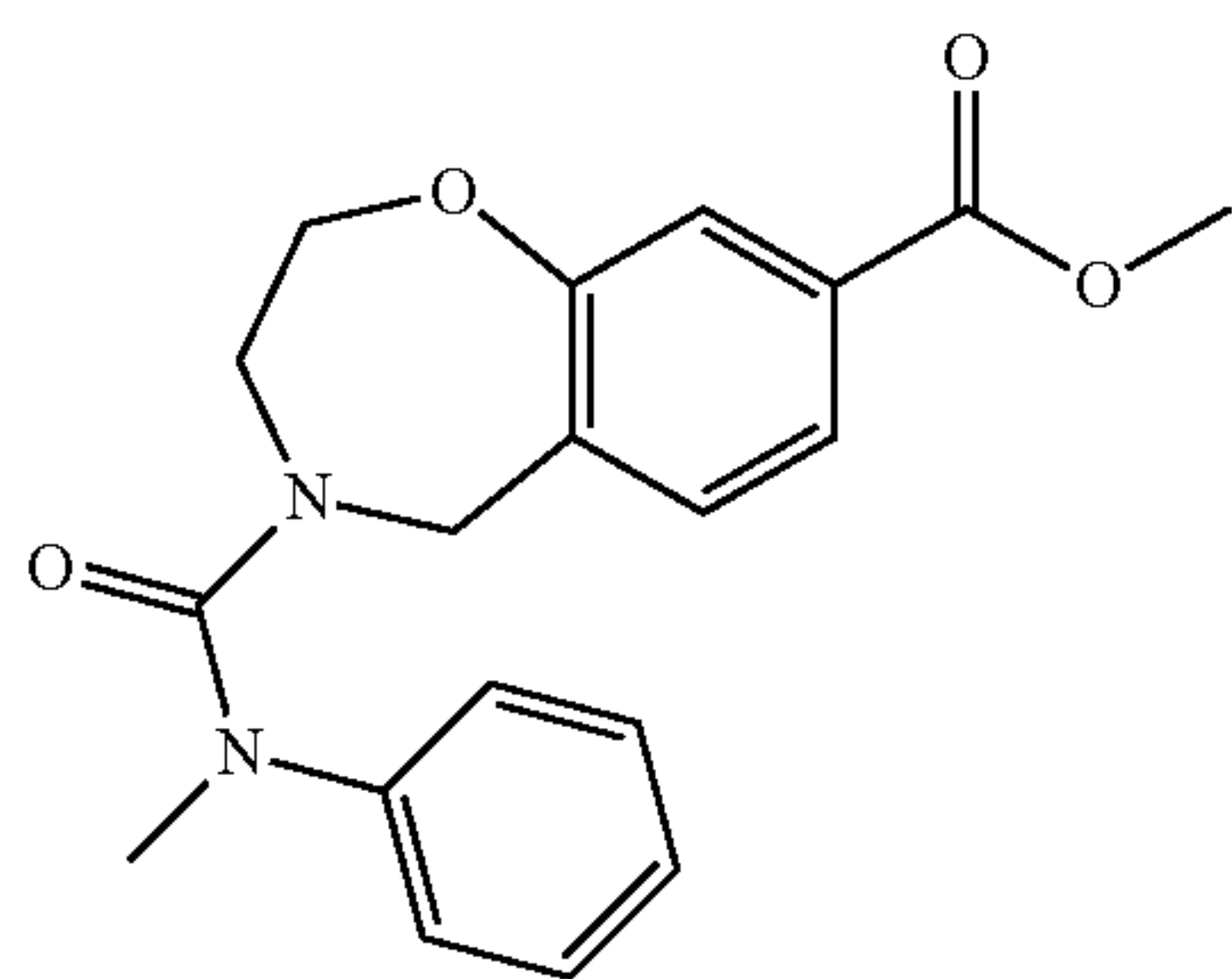
The following compounds were prepared according to the method of Example 5.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 356 [M + H] <sup>+</sup>	11.22 (s, 1H), 9.02-9.06 (br s, 1H), 7.31-7.42 (m, 3H), 4.47 (s, 2H), 4.14-4.17 (m, 2H), 3.64-3.66 (m, 2H), 3.01-3.02 (m, 4H), 1.44 (m, 6H)

## Example 6

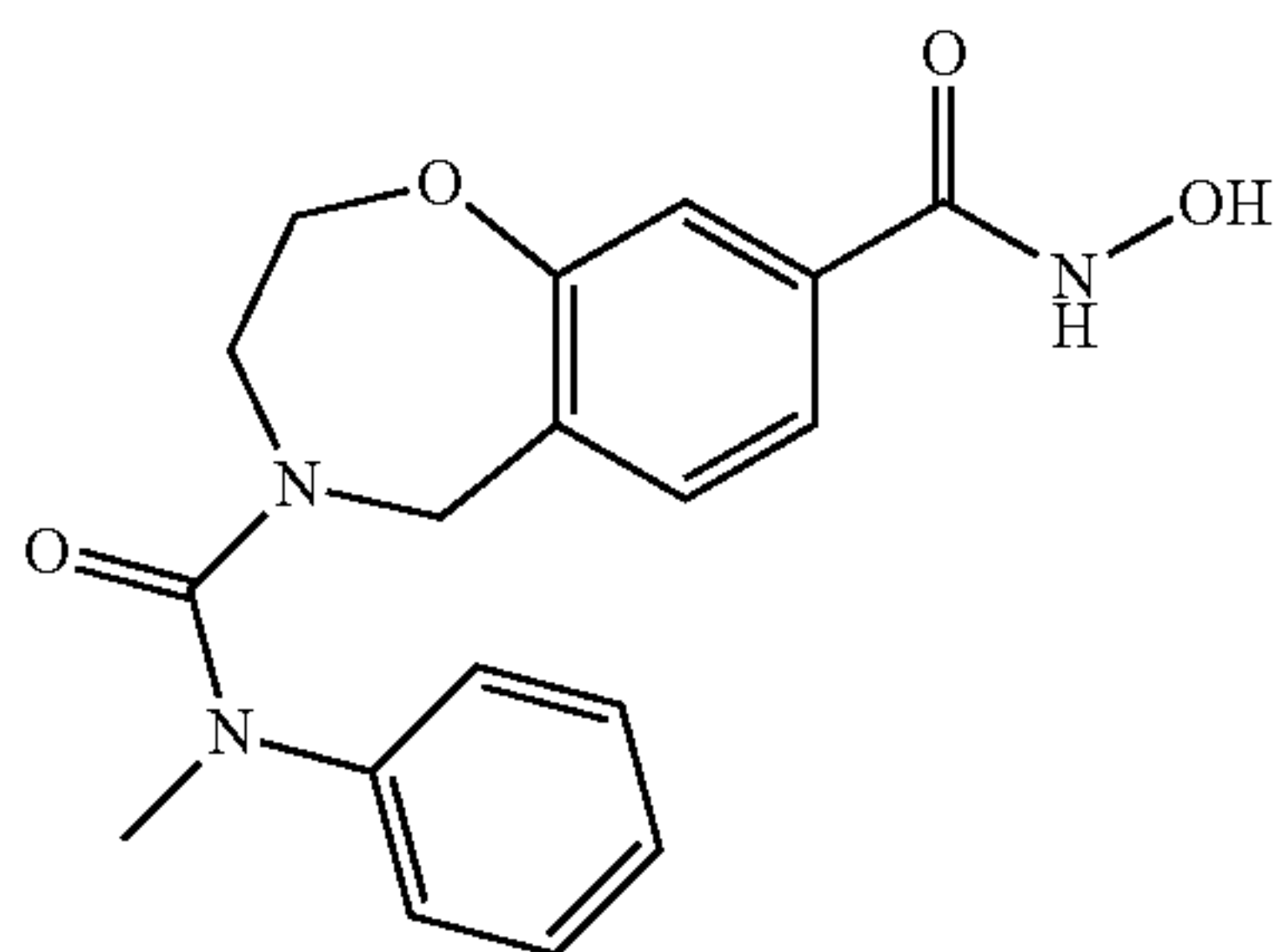
Preparation of N8-hydroxy-N4-methyl-N4-phenyl-  
2,3,7,8-tetrahydrobenzo[f][1,4]oxazepine-4,8(5H)-  
dicarboxamide



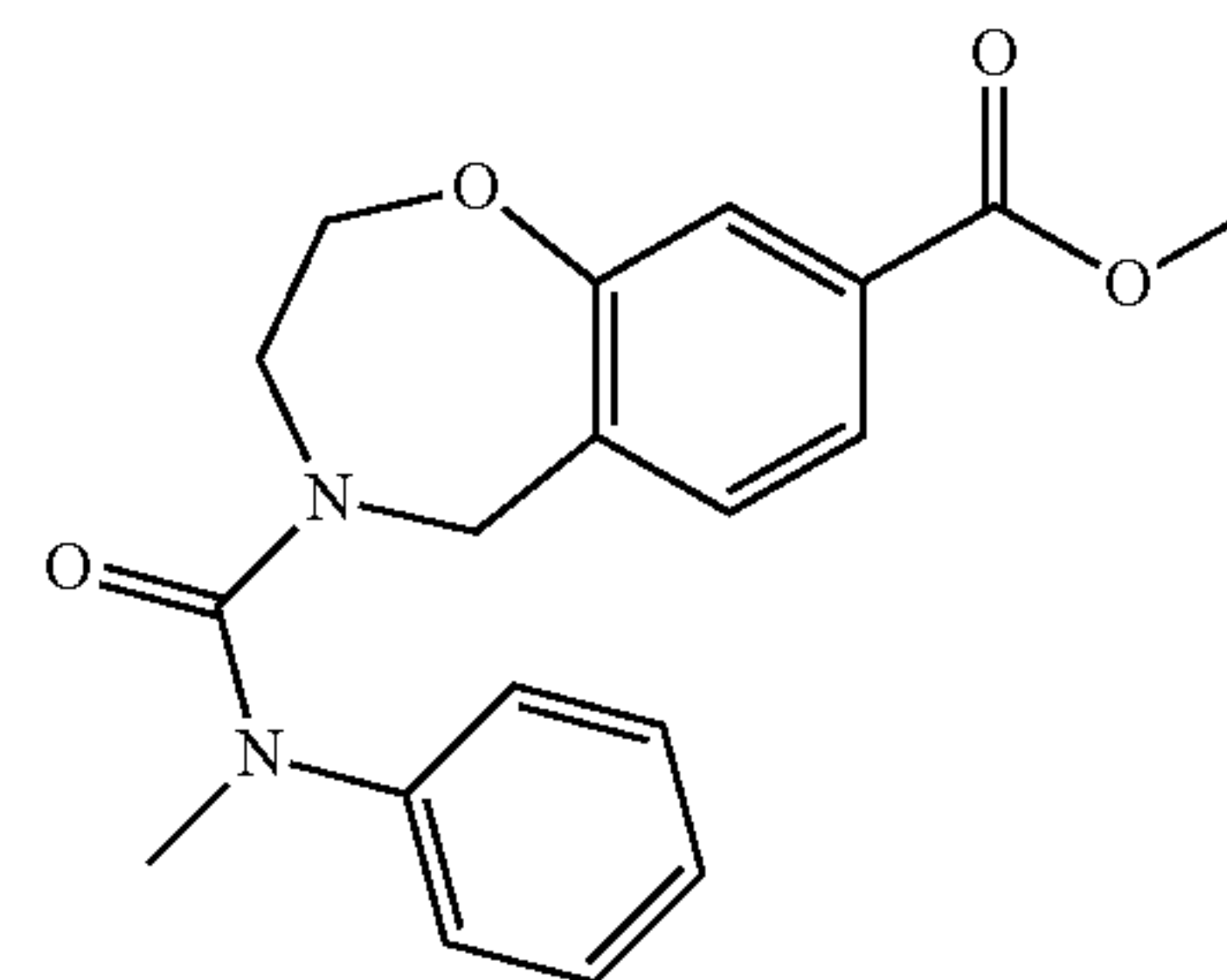
step 1



step 2

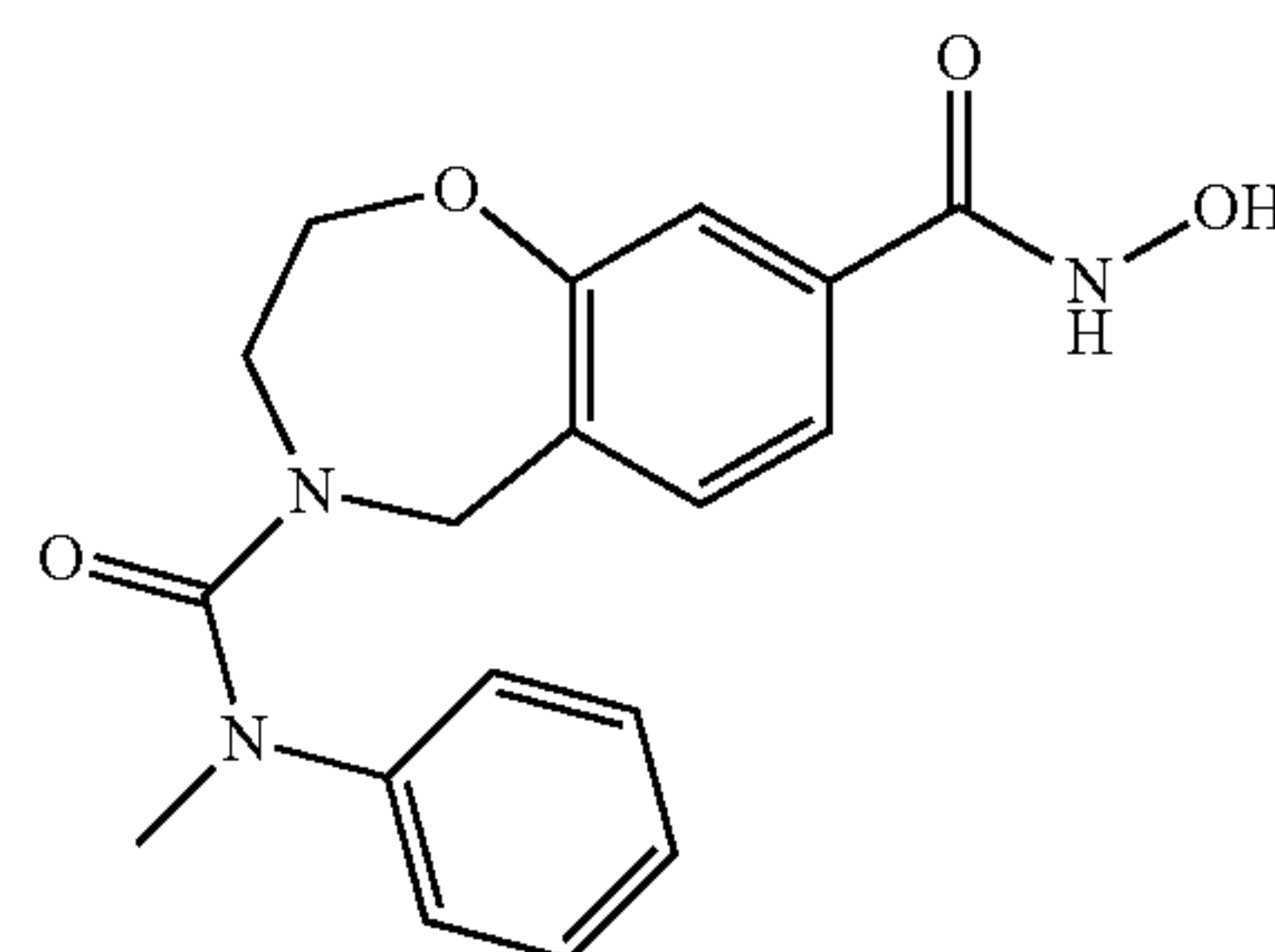


Step-1: Methyl 4-(methyl(phenyl)carbamoyl)-2,3,4,  
5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 25-mL round-bottom flask purged and maintained  
with an inert atmosphere of nitrogen, was placed a solution  
of N-methylaniline (26 mg, 0.24 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub>  
(5 mL). This was followed by the addition of ditrichlorom-  
ethyl carbonate (25 mg, 0.08 mmol, 0.35 equiv) dropwise  
with stirring. Et<sub>3</sub>N (61 mg, 0.60 mmol, 2.5 equiv) was added  
and the resulting mixture was stirred for 10 minutes at room  
temperature. Methyl 2,3,4,5-tetrahydrobenzo[f][1,4]ox-  
azepine-8-carboxylate (50 mg, 0.24 mmol, 1 equiv) was  
added and the resulting solution was stirred for an additional  
30 min at room temperature. The reaction was then  
quenched by the addition of sat. aq. NaHCO<sub>3</sub> solution (10  
mL). The crude residue was purified by Prep-TLC to afford  
the title compound as a light yellow solid (25 mg, 30%  
yield). MS: (ES, m/z): 340 [M+H]<sup>+</sup>.

Step-2: N8-Hydroxy-N4-methyl-N4-phenyl-2,3,7,8-  
tetrahydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarbox-  
amide



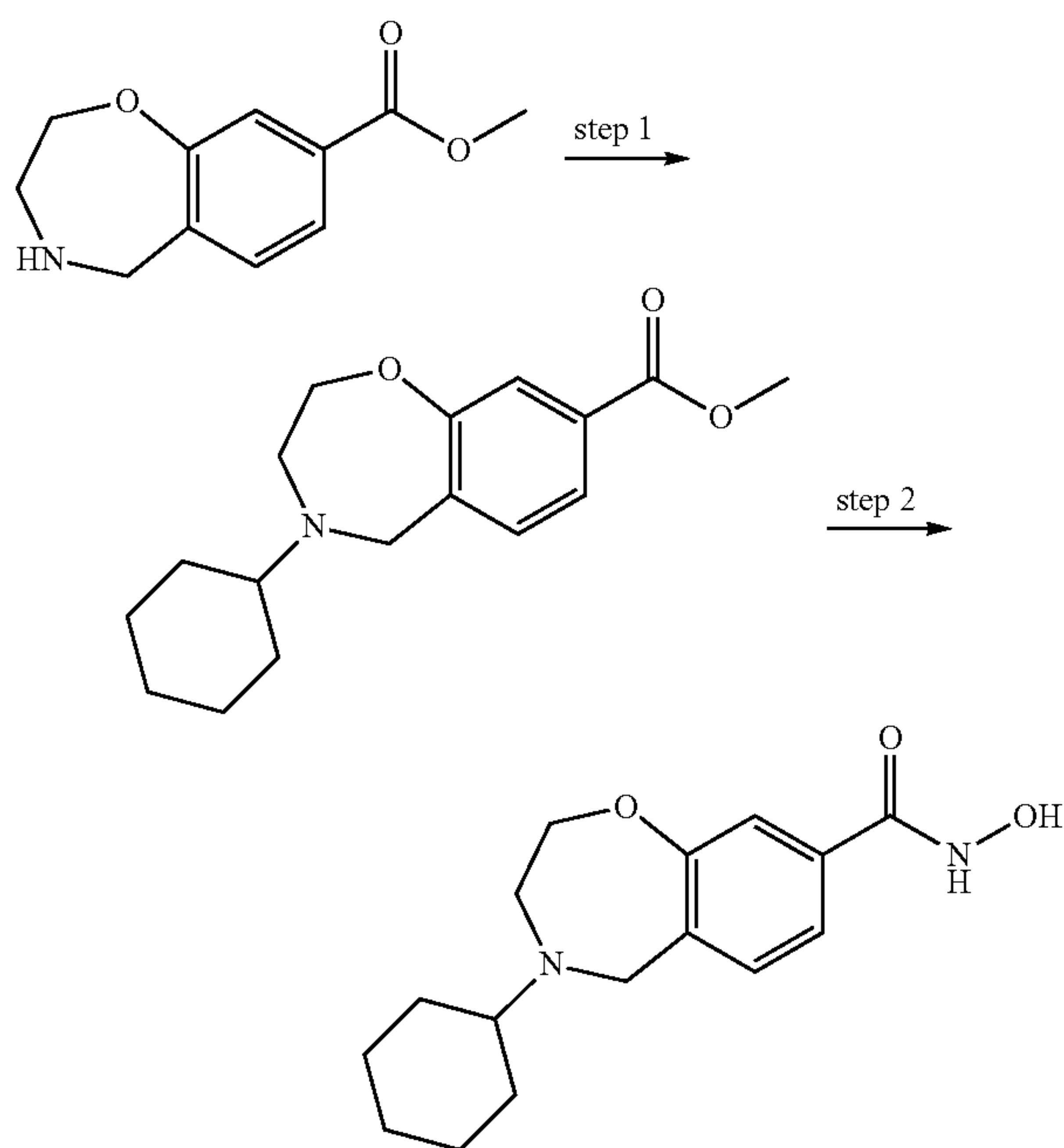


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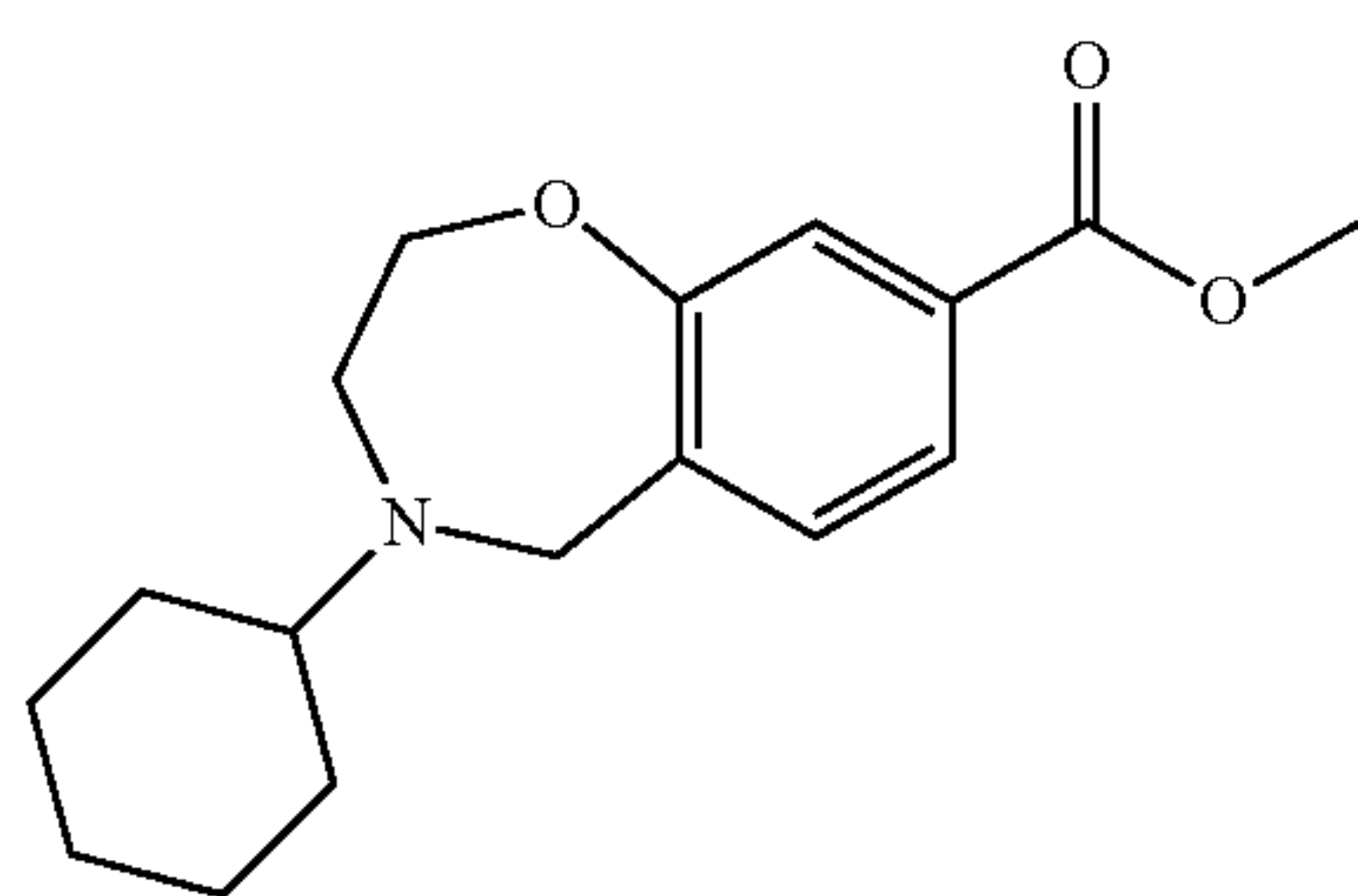
Into a 25-mL round-bottom flask was placed a solution of methyl 4-(methyl(phenyl)carbamoyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (65 mg, 0.19 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL). This was followed by the addition of  $\text{NH}_2\text{OH}$  (50% in water, 0.35 mL, 30 equiv) dropwise with stirring. To this was added aq. 1N NaOH (0.57 mL, 3 equiv). The resulting solution was stirred for 30 min at room temperature. The pH value of the solution was adjusted to 5-6 with 1N HCl. The crude product was purified by Prep-HPLC (Column: XBridge RP C18 OBD, 5  $\mu\text{m}$ , 19 $\times$ 150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 5% B to 44% B in 7 min; Detector: UV 254 nm) to afford the title compound as a pink solid (61 mg, 94% yield).  $^1\text{H}$ -NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.16 (s, 1H), 7.23-7.33 (m, 3H), 7.14 (s, 1H), 7.01-7.09 (m, 3H), 6.99 (d, 1H), 4.35 (s, 2H), 4.04-4.07 (s, 2H), 3.40-3.43 (s, 2H), 3.03 (s, 3H). MS: (ES,  $m/z$ ): 341  $[\text{M}+\text{H}]^+$ .

## Example 7

Preparation of 4-cyclohexyl-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



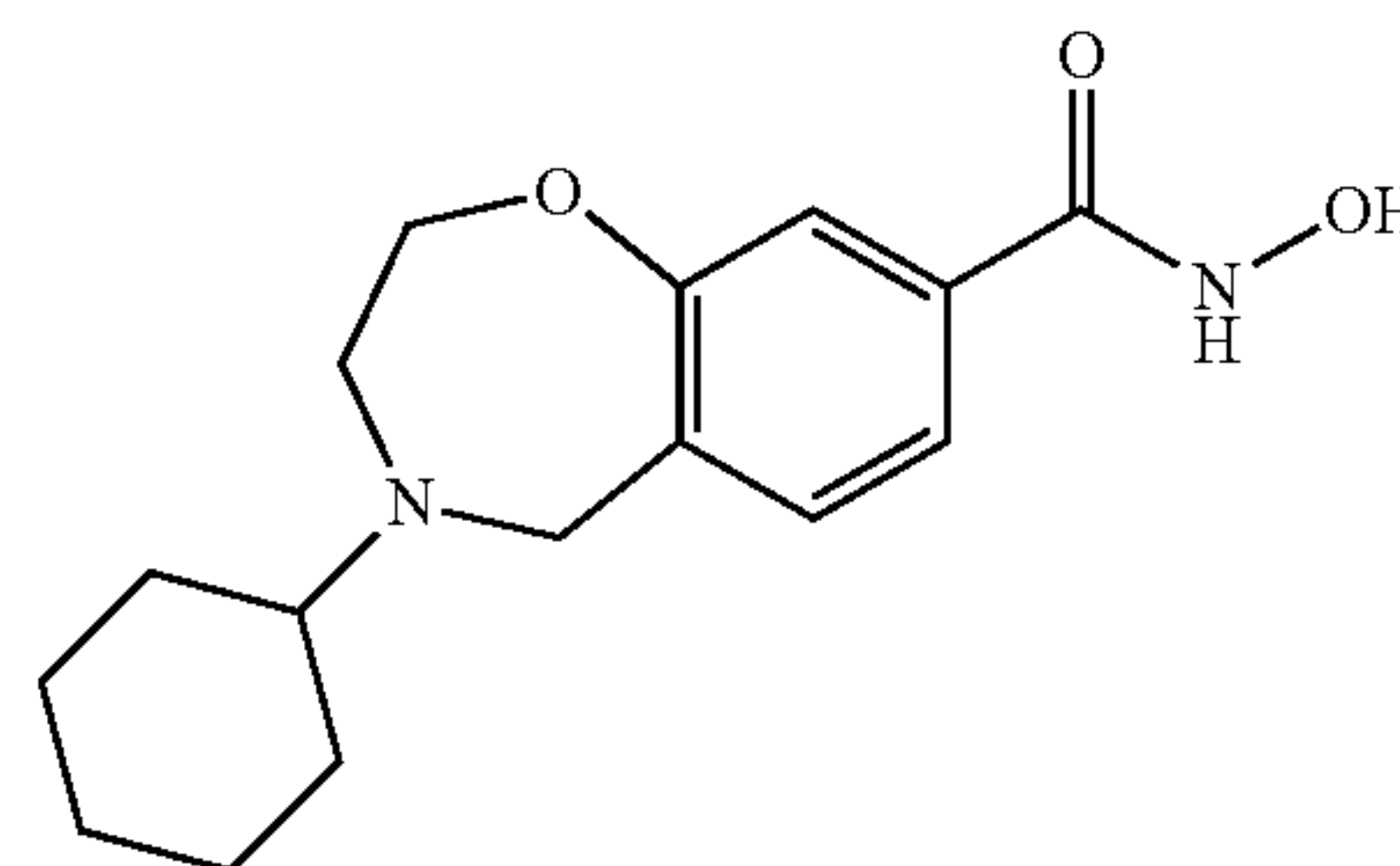
Step-1: Methyl 4-cyclohexyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



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Into a 25-mL round-bottom flask, was placed methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (206 mg, 0.99 mmol, 1 equiv),  $\text{CH}_2\text{Cl}_2$  (8 mL) and cyclohexanone (106 mg, 1.08 mmol, 1.1 equiv). The solution was stirred for 1 h at room temperature. Then to this was added  $\text{NaBH}(\text{OAc})_3$  (2.15 g, 10.14 mmol, 10 equiv). The resulting solution was stirred for 4 h at room temperature. The reaction mixture was cooled to  $0^\circ\text{C}$ . with a water/ice bath. The reaction was then quenched by the addition of water (20 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ 50 mL). The organic phase was washed with sat. aq.  $\text{NaHCO}_3$  solution (50 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to afford the title compound as brown oil (80 mg) which was used without further purification. MS: (ES,  $m/z$ ): 289  $[\text{M}+\text{H}]^+$ .

Step-2: 4-Cyclohexyl-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 25-mL round-bottom flask, was placed a solution of methyl 4-cyclohexyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (140 mg, 0.48 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), aq. 1N NaOH (0.969 mL, 2 equiv) and  $\text{NH}_2\text{OH}$  (50% in water, 959 mg, 30 equiv). The resulting solution was stirred for 2 h at room temperature. The pH value of the solution was adjusted to 6 with 2N HCl. The crude product was purified by Prep-HPLC (Column: HSS C18 OBD, 1.8  $\mu\text{m}$ , 2.1 $\times$ 50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2 min, hold 0.6 min; Detector: UV 254, 220 nm) to afford the title compound as an orange solid (35 mg, 18% yield).  $^1\text{H}$ -NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.33 (s, 1H), 9.98 (s, 1H), 9.15 (s, 1H), 7.54 (s, 2H), 7.44 (s, 1H), 4.49-4.64 (m, 2H), 4.09-4.14 (t,  $J=12.8$  Hz, 1H), 3.65-3.70 (d,  $J=20.4$  Hz, 2H), 3.39 (s, 1H), 2.02-2.12 (m, 2H), 1.83-1.85 (d,  $J=11.6$  Hz, 2H), 1.46-1.64 (m, 3H), 1.21-1.31 (m, 3H). MS: (ES,  $m/z$ ): 290  $[\text{M}+\text{H}]^+$ .

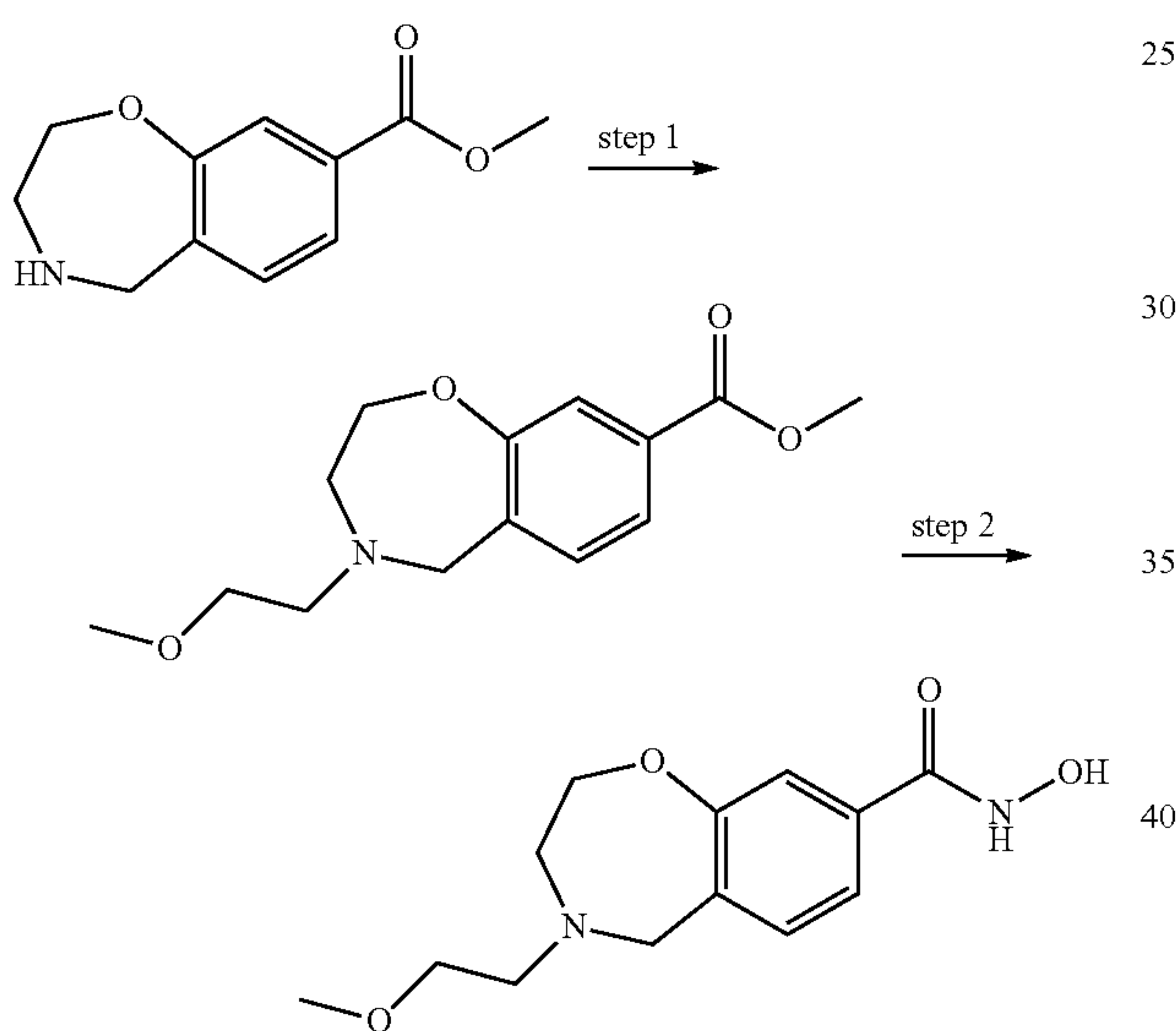


TABLE 5

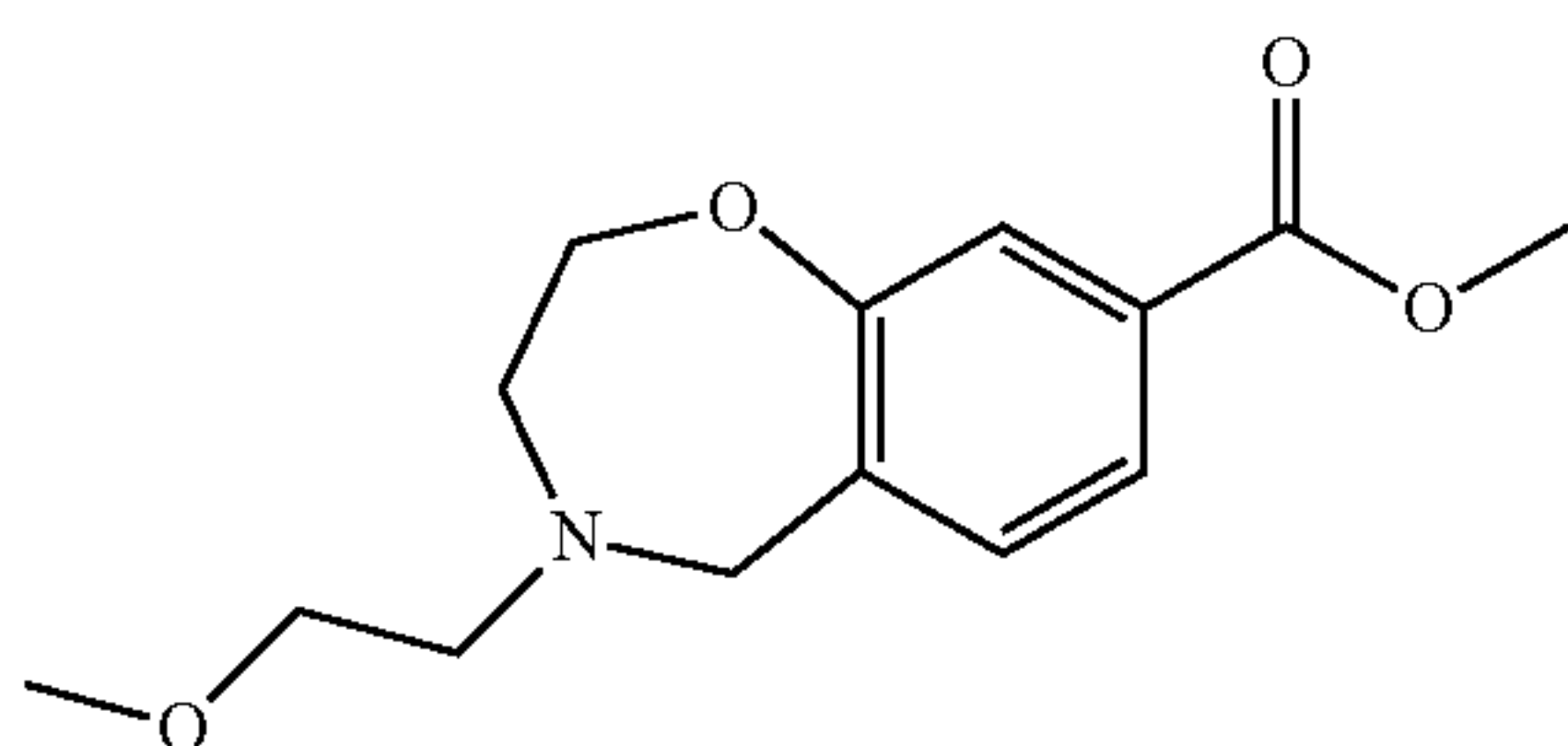
The following compounds were prepared according to the method of Example 7.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 280 [M + H] <sup>+</sup>	11.21 (s, 1H), 10.10 (s, 1H), 7.37-7.45 (m, 3H), 4.05-4.15 (d, J = 37.2 Hz, 2H), 3.94 (s, 2H), 3.21-3.24 (m, 2H), 3.14 (s, 2H), 2.74-2.78 (m, 8H)

## Example 8

Preparation of N-hydroxy-4-(2-methoxyethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



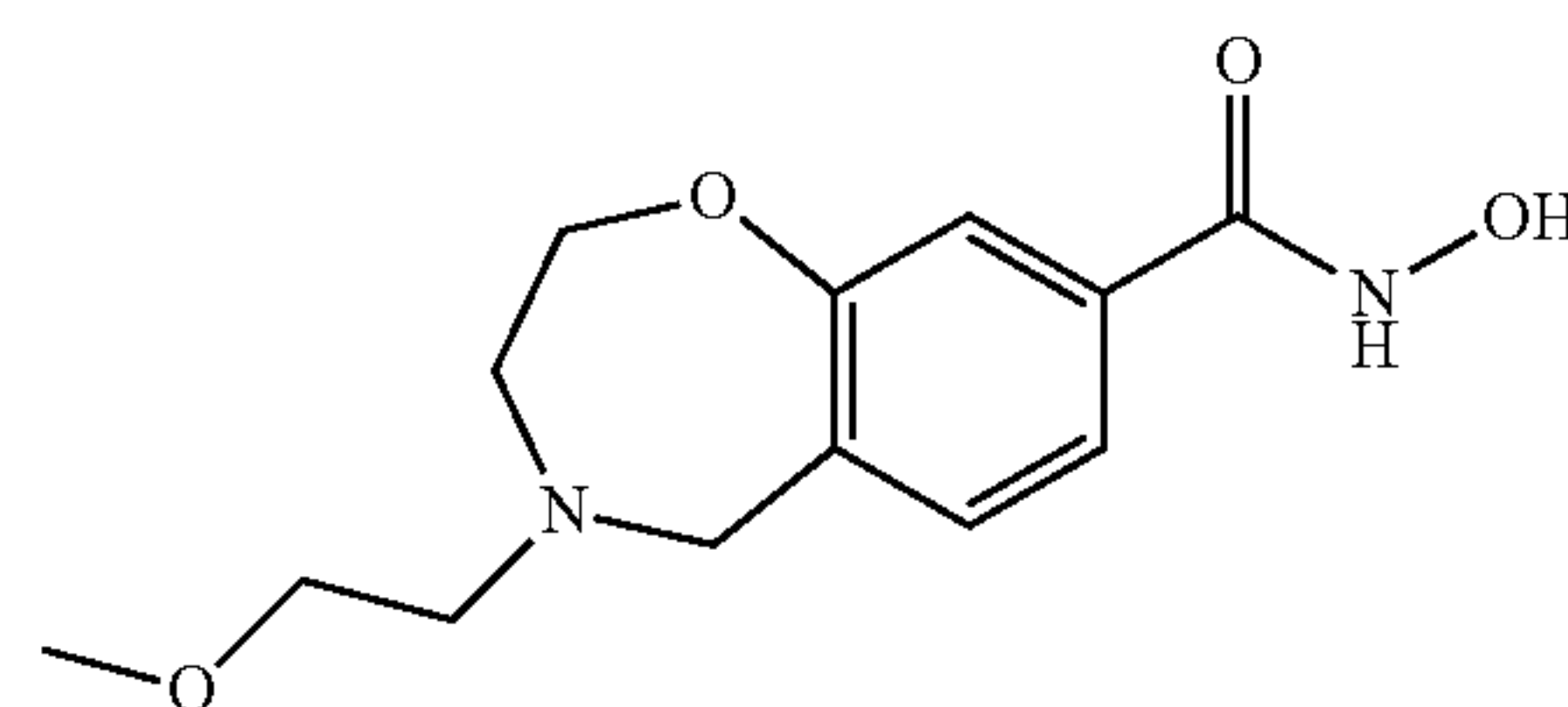
Step-1: Methyl 4-(2-methoxyethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 10-mL round-bottom flask, was placed a solution of methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (104 mg, 0.50 mmol, 1 equiv) in DMF (2 mL), K<sub>2</sub>CO<sub>3</sub> (138.1 mg, 1 mmol, 2 equiv) and 1-iodo-2-methoxyethane (102.8 mg, 0.55 mmol, 1.1 equiv). The resulting solution was stirred overnight at room temperature. The

reaction was then quenched by the addition of water (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:10) to afford the title compound as a yellow oil (46 mg). MS: (ES, m/z): 266 [M+H]<sup>+</sup>.

Step-2: N-Hydroxy-4-(2-methoxyethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



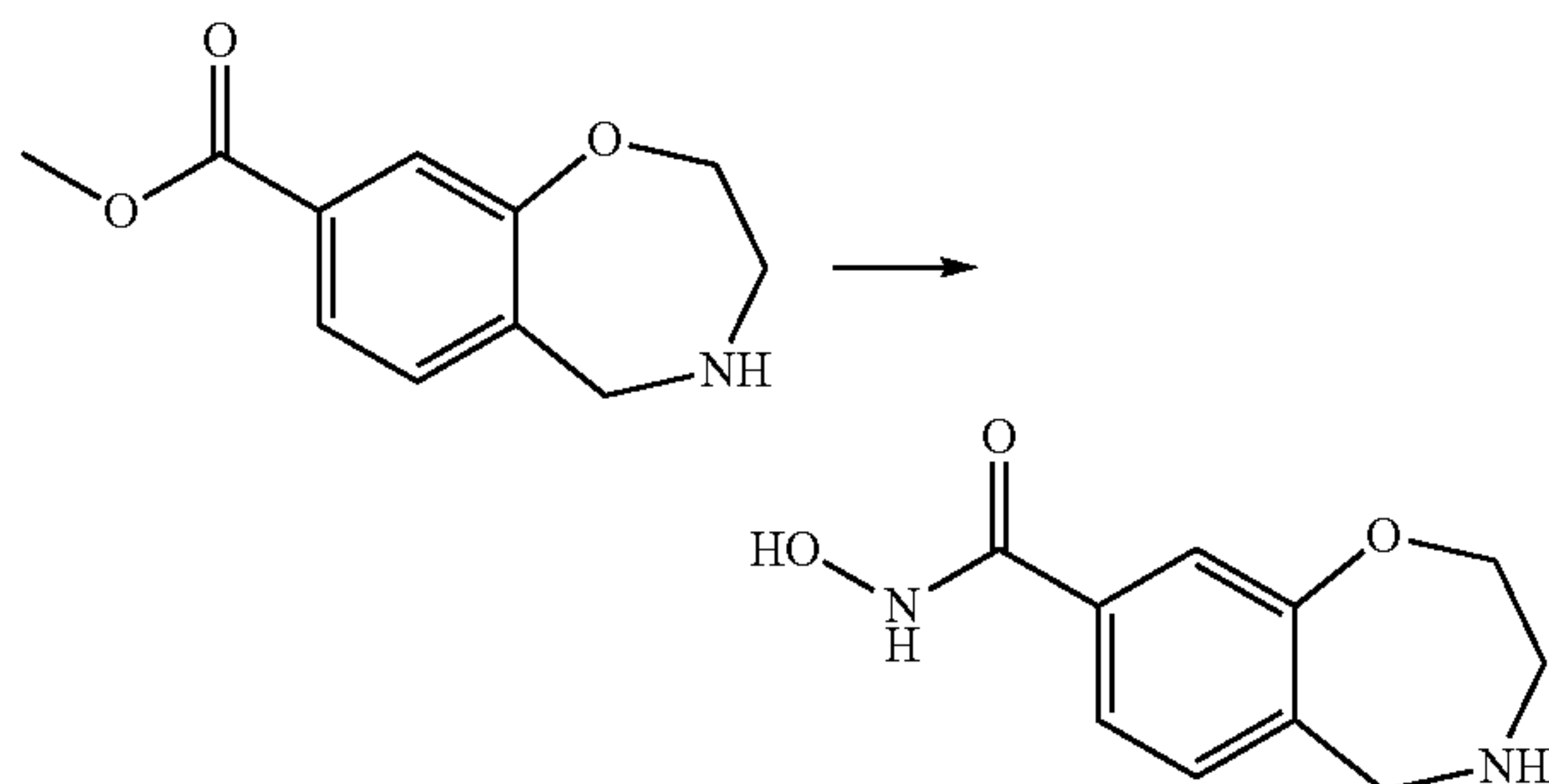
Into a 25-mL round-bottom flask, was placed a solution of methyl 4-(2-methoxyethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (46 mg, 0.17 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), aq. 1N NaOH (0.347 mL, 2 equiv) and NH<sub>2</sub>OH (50% in water, 343.7 mg, 10.42 mmol, 30 equiv). The resulting solution was stirred for 2 h at room temperature. The pH value of the solution was adjusted to 6 with 2N HCl. The crude product was purified by Prep-HPLC (Column: HSS C18 OBD, 1.8 μm, 2.1×50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2 min, hold 0.6 min; Detector: UV 254, 220 nm) to afford the title compound as an orange solid (29 mg, 44% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.31 (s, 1H), 10.29 (s, 1H), 9.15 (s, 1H), 7.50-7.55 (m, 2H), 7.44 (s, 1H), 4.24-4.51 (m, 4H), 3.69 (s, 4H), 3.34 (s, 3H). MS: (ES, m/z): 267[M+H]<sup>+</sup>.



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## Example 9

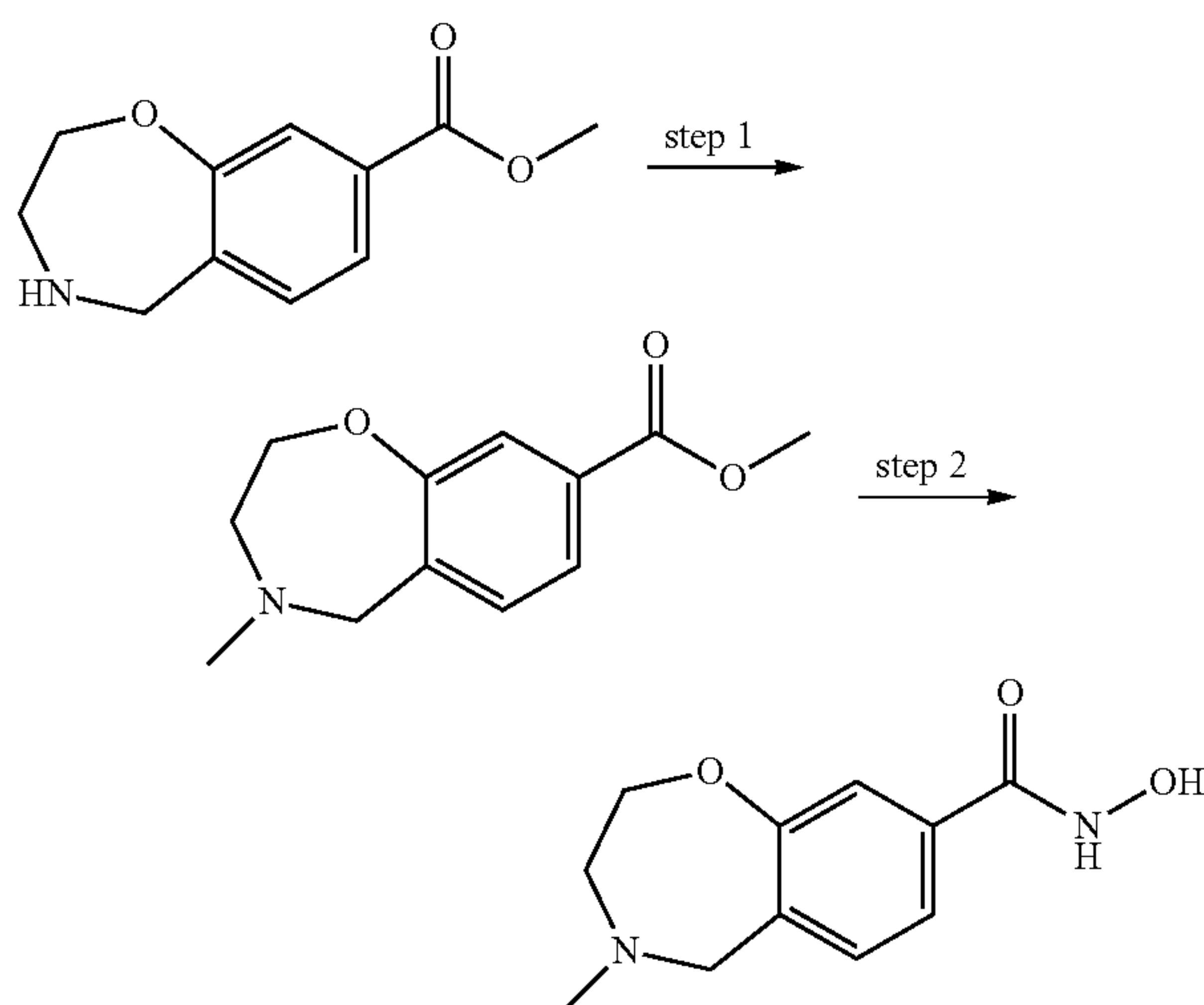
Preparation of N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide 2,2,2-trifluoroacetate



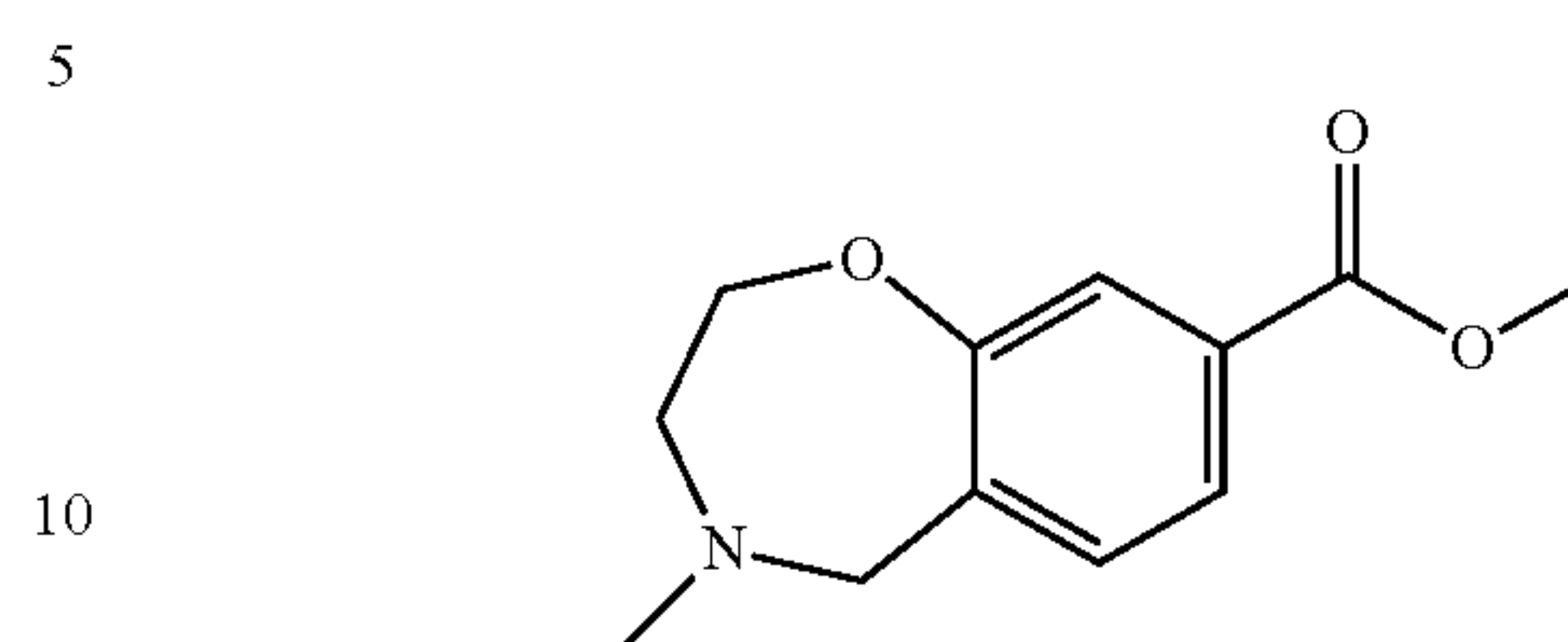
Into a 8-mL vial, was placed methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (60 mg, 0.29 mmol, 1 equiv) in THF/MeOH (4:1, 1.5 mL), aq. 1N NaOH (0.58 mL, 0.58 mmol, 2 equiv) and  $\text{NH}_2\text{OH}$  (50% in water, 0.58 mL, 8.69 mmol, 30 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge RP C18 OBD, 5  $\mu\text{m}$ , 19 $\times$ 150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 4% B to 58% B in 7 min; Detector: UV 254, 220 nm) to afford the title compound as a pink solid (21 mg, 23% yield).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.29 (s, 1H), 9.42 (br s, 2H), 9.11 (s, 1H), 7.48-7.52 (m, 2H), 7.42-7.45 (s, 1H), 4.37 (s, 2H), 4.21-4.23 (m, 2H), 3.49-3.51 (m, 2H). MS: (ES, m/z): 209  $[\text{M}+\text{H}]^+$ .

## Example 10

Preparation of N-hydroxy-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide 2,2,2-trifluoroacetate

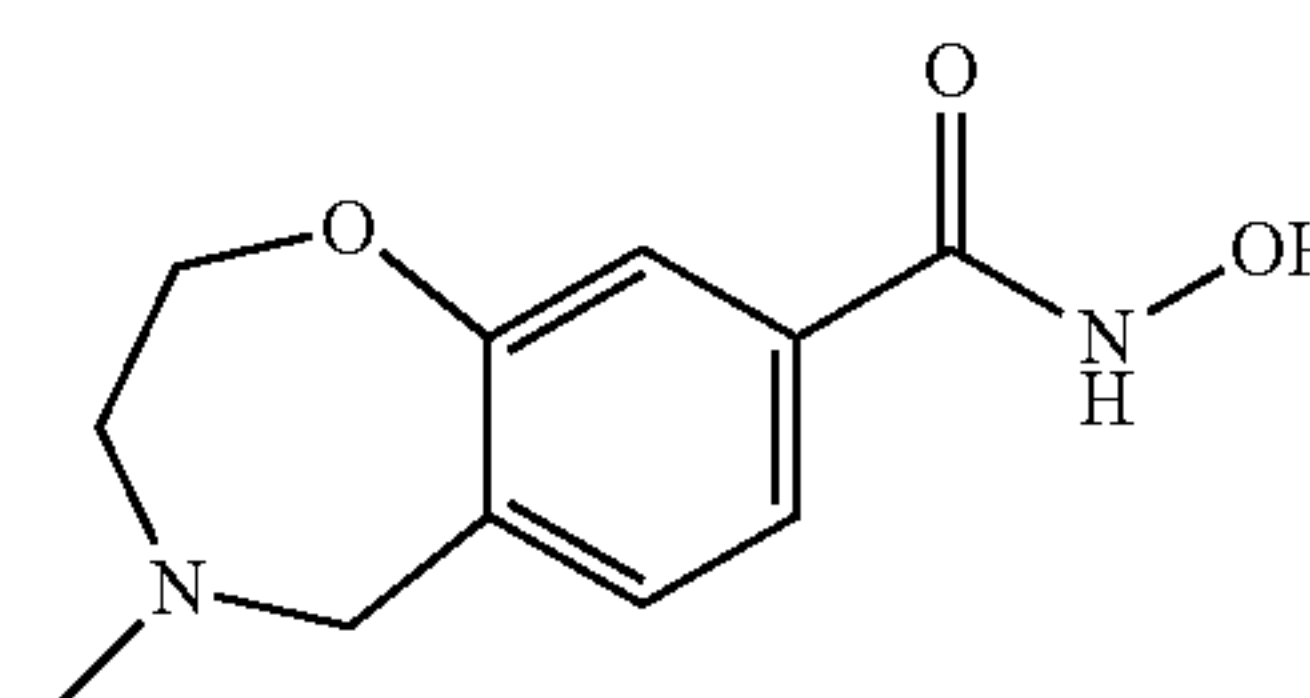
**62**

Step-1: Methyl 4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 25-mL round-bottom flask, was placed methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.31 mmol, 1 equiv), acetic acid (3 mL) and paraformaldehyde (28 mg, 0.93 mmol, 3 equiv). The resulting mixture was stirred for 2 h at room temperature. Then acetyl ethaneperoxoate sodioboranyl acetate (327 mg, 1.54 mmol, 5 equiv) was added and the reaction was stirred for an additional 18 h at room temperature. The resulting mixture was concentrated under vacuum, diluted with EtOAc (50 mL), washed with  $\text{H}_2\text{O}$  (3 $\times$ 25 mL), dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated to afford the title compound as a yellow solid (100 mg) which was used without further purification. MS: (ES, m/z): 222  $[\text{M}+\text{H}]^+$ .

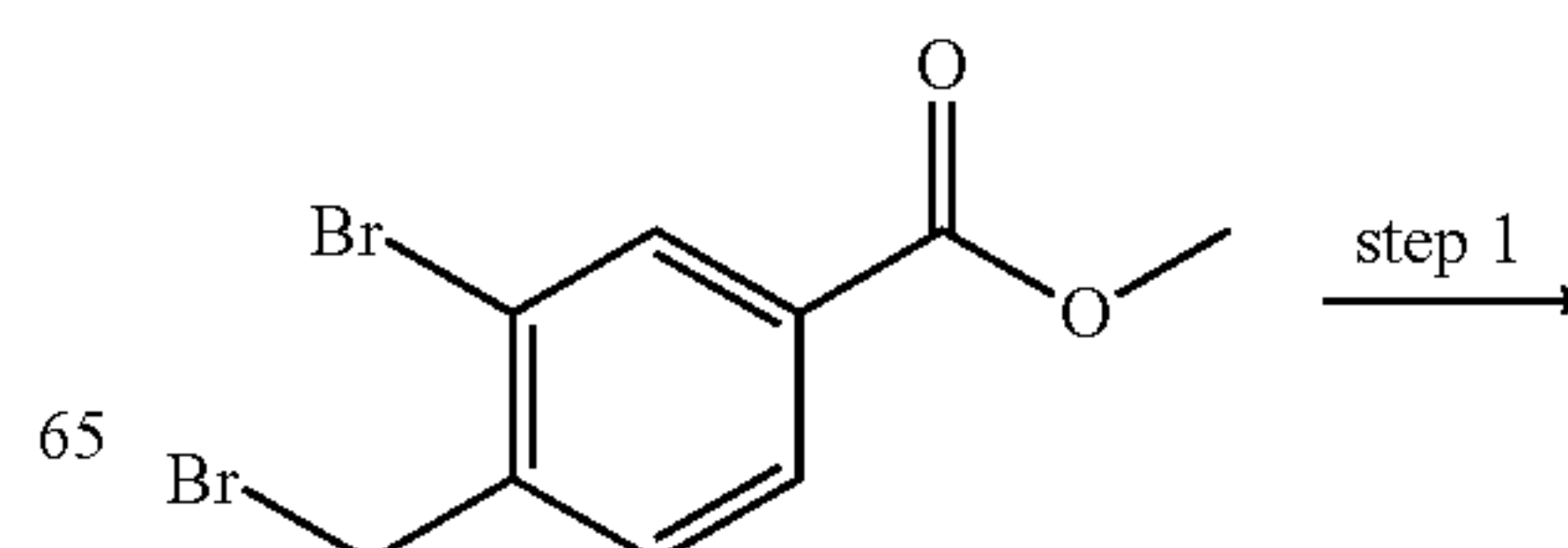
Step-2: N-Hydroxy-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide 2,2,2-trifluoroacetate



Into a 8-mL vial, was placed methyl 4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv) in THF/MeOH (4:1, 1 mL), aq. 1N NaOH (0.9 mL, 0.90 mmol, 2 equiv) and  $\text{NH}_2\text{OH}$  (50% in water, 0.9 mL, 13.56 mmol, 30 equiv). The resulting solution was stirred for 1 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge RP C18 OBD, 5  $\mu\text{m}$ , 19 $\times$ 150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 4% B to 58% B in 7 min; Detector: UV 254, 220 nm) to afford the title compound as a yellow oil (45 mg, 29% yield).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.31 (s, 1H), 10.54 (s, 1H), 9.91 (s, 1H), 7.42-7.54 (m, 3H), 4.48 (s, 1H), 4.26 (s, 2H), 3.62 (s, 2H), 3.88 (s, 3H). MS: (ES, m/z): 223  $[\text{M}+\text{H}]^+$ .

## Example 11

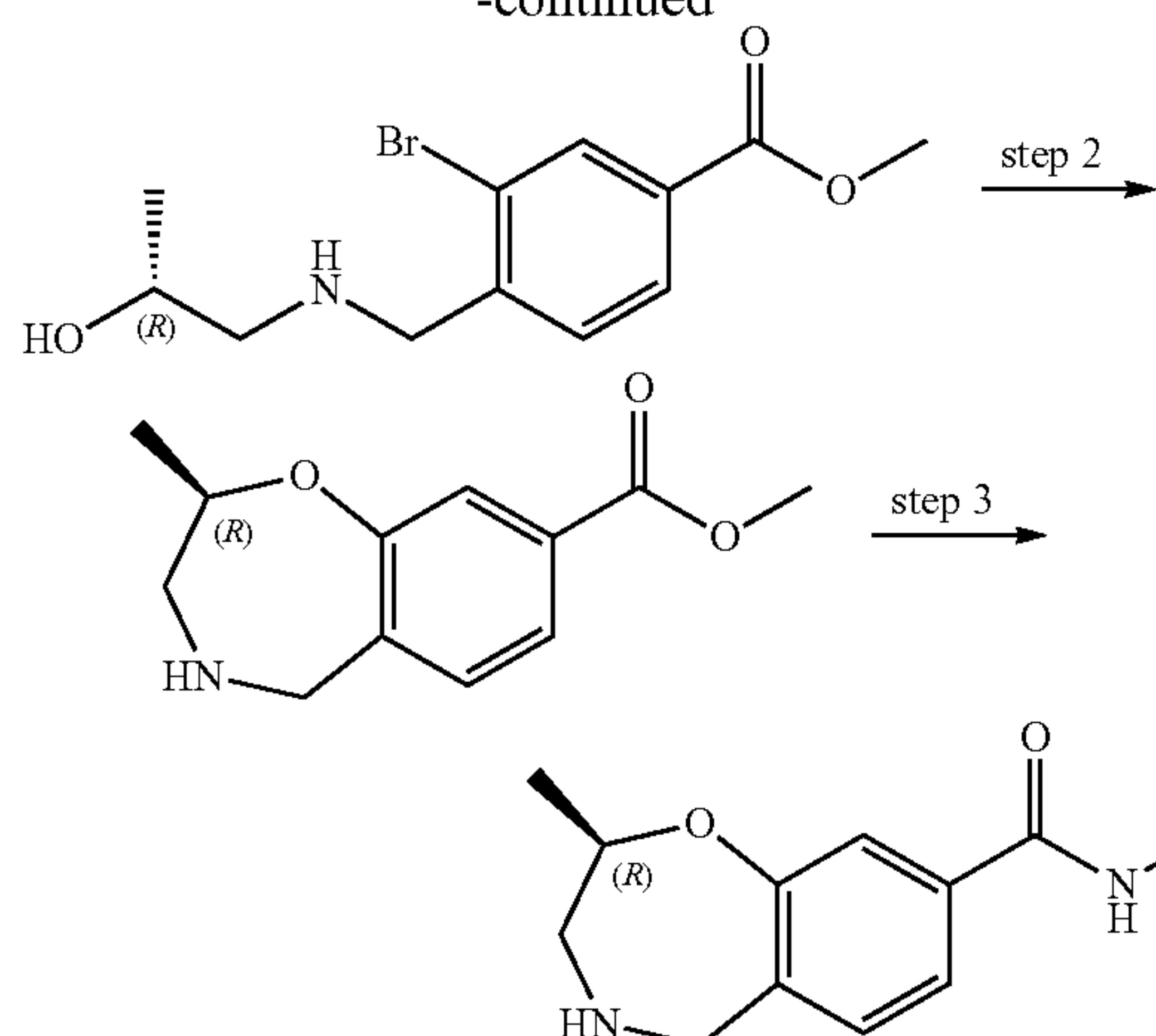
Preparation of (R)—N-hydroxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



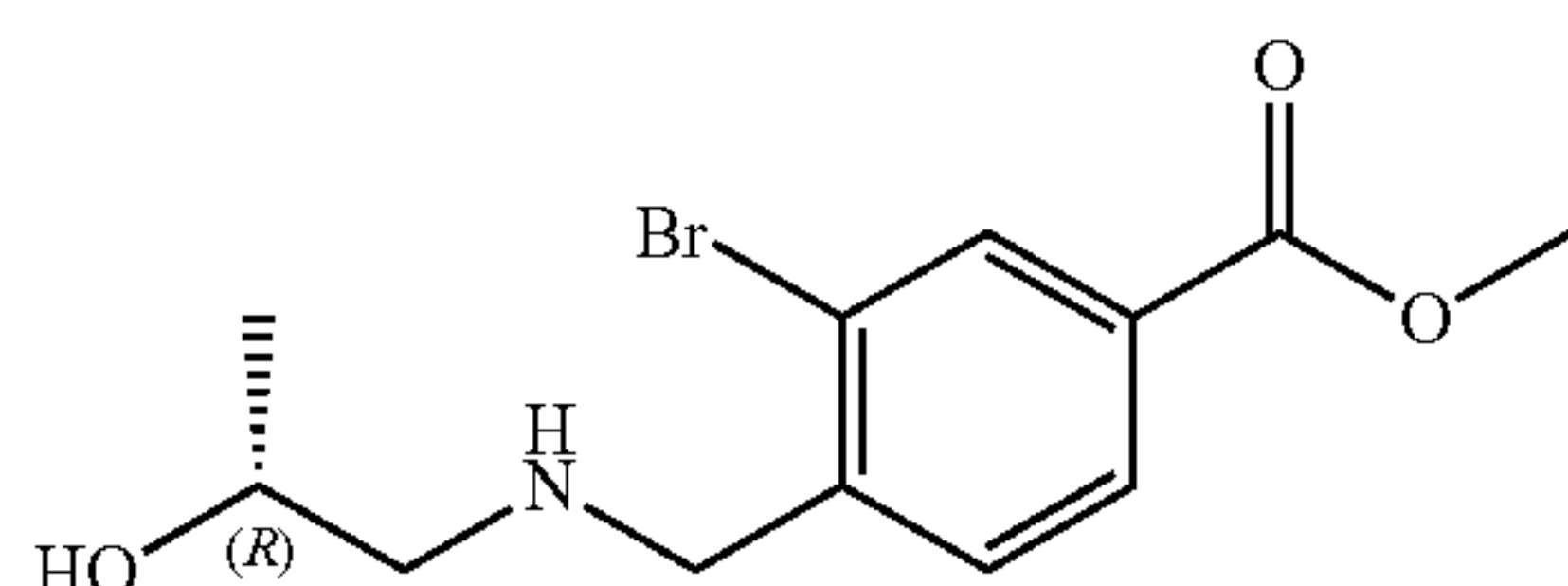


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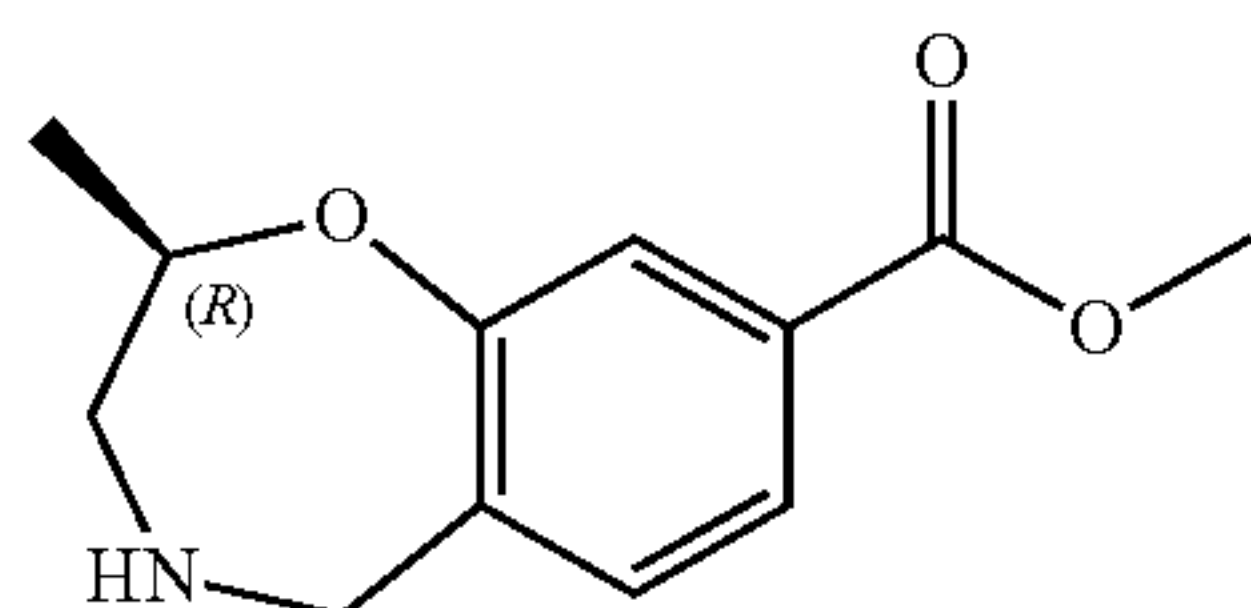


Step-1: Methyl (R)-3-bromo-4-(((2-hydroxypropyl)amino)methyl)benzoate



Into a 250-mL round-bottom flask, was placed a solution of methyl 3-bromo-4-(bromomethyl)benzoate (7 g, 22.73 mmol, 1 equiv) in MeCN (80 mL), potassium carbonate (4.69 g, 33.93 mmol, 1.50 equiv) and (2R)-1-aminopropan-2-ol (1.7 g, 22.63 mmol, 1 equiv). The resulting mixture was stirred for 3 h at room temperature and then concentrated under vacuum. The residue was diluted with EtOAc (80 mL) and the resulting solution was washed with water (3×30 mL). The organic phase was concentrated under vacuum to afford the title compound as an off-white solid (3 g) which was used without further purification. MS: (ES, m/z): 302 [M+H]<sup>+</sup>.

Step-2: Methyl (R)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

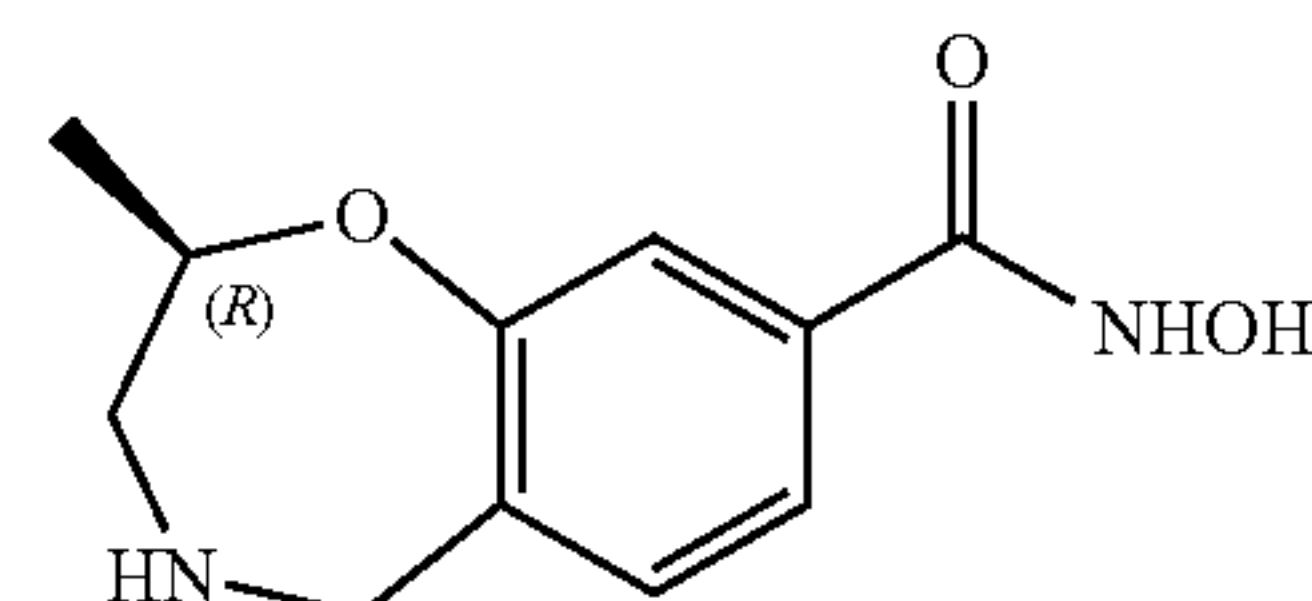


Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl (R)-3-bromo-4-(((2-hydroxypropyl)amino)methyl)benzoate (2.75 g, 9.10 mmol, 1 equiv) in isopropanol (32 mL), potassium carbonate (2.53 g, 18.31 mmol, 2 equiv) and CuI (520 mg, 2.73 mmol, 0.30 equiv). The resulting solution was stirred for 21 h at 110° C. in an oil bath. The resulting mixture was concentrated under vacuum and the residue was diluted with EtOAc (100 mL). The resulting

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mixture was washed with water (3×150 mL) and the organic phase was concentrated, then the residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 99:1) to afford the title compound as a brown oil (1.1 g, 55% yield). MS: (ES, m/z): 222 [M+H]<sup>+</sup>.

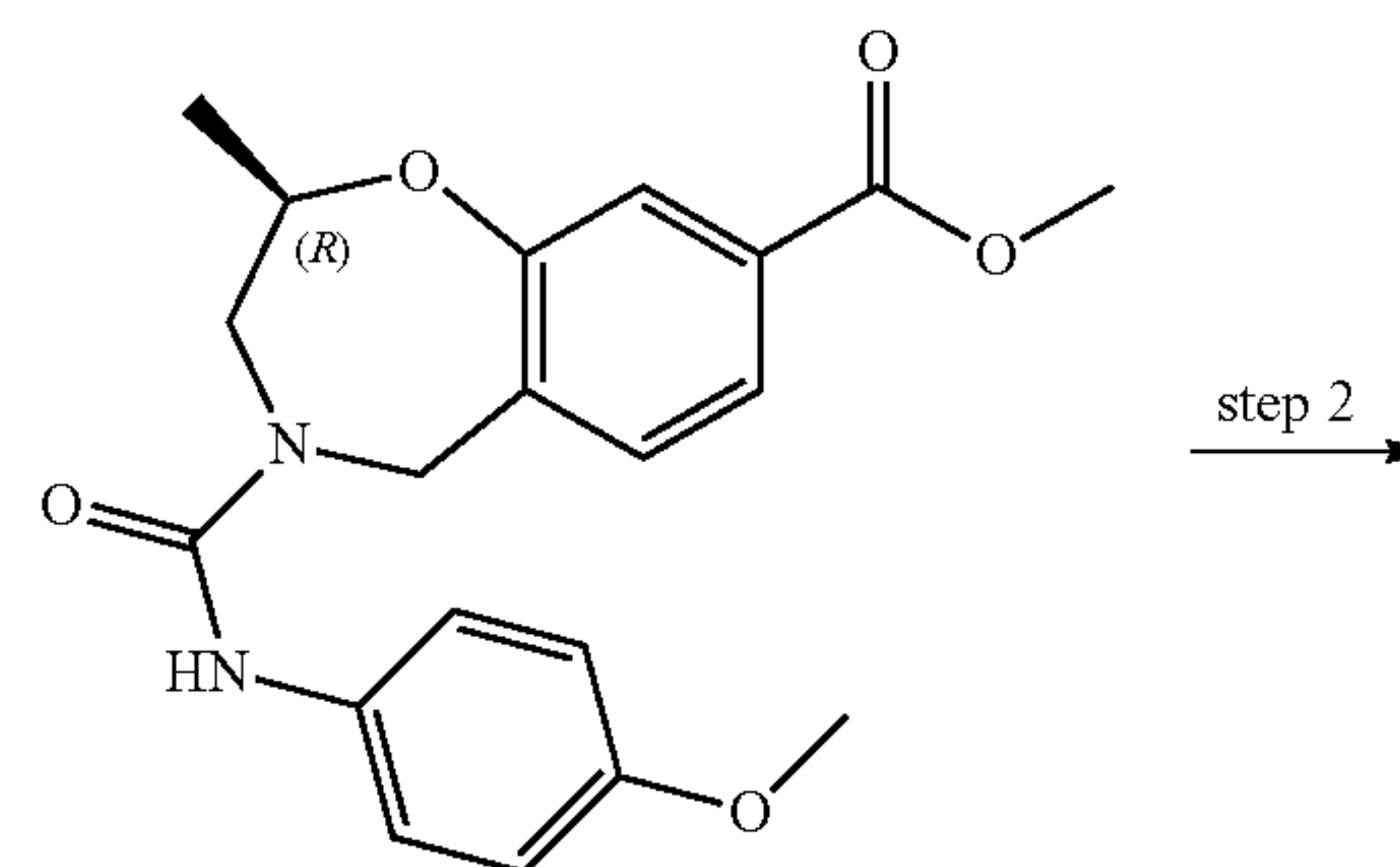
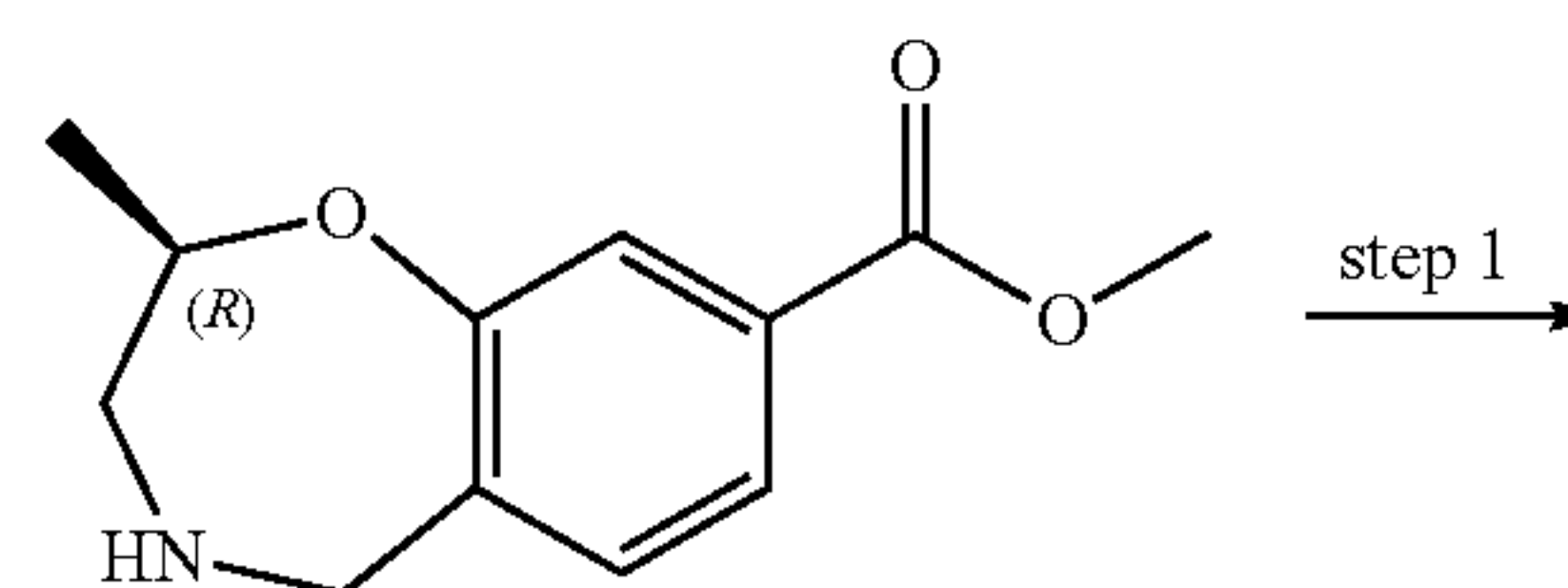
Step-3: (R)—N-Hydroxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed a solution of methyl (R)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (50 mg, 0.23 mmol, 1 equiv) in THF/MeOH (4:1, 1 mL), NH<sub>2</sub>OH (50% in water, 0.44 mL, 30 equiv) and aq. 1N NaOH (0.45 mL, 2 equiv). The resulting solution was stirred for 14 h at room temperature. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 4% B to 18% B in 6 min; Detector: UV 254, 220 nm) to afford the title compound as a brown oil (15 mg, 21% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.28 (s, 1H), 9.24 (br s, 2H), 7.56-7.33 (m, 3H), 4.45-4.38 (d, J=7.2 Hz, 1H), 4.31-4.28 (d, J=7.2 Hz, 1H), 4.18-4.11 (m, 1H), 3.53-3.49 (d, J=6.4 Hz, 1H), 3.29-3.28 (m, 1H), 1.39-1.37 (m, 3H). MS: (ES, m/z): 223 [M+H]<sup>+</sup>.

### Example 12

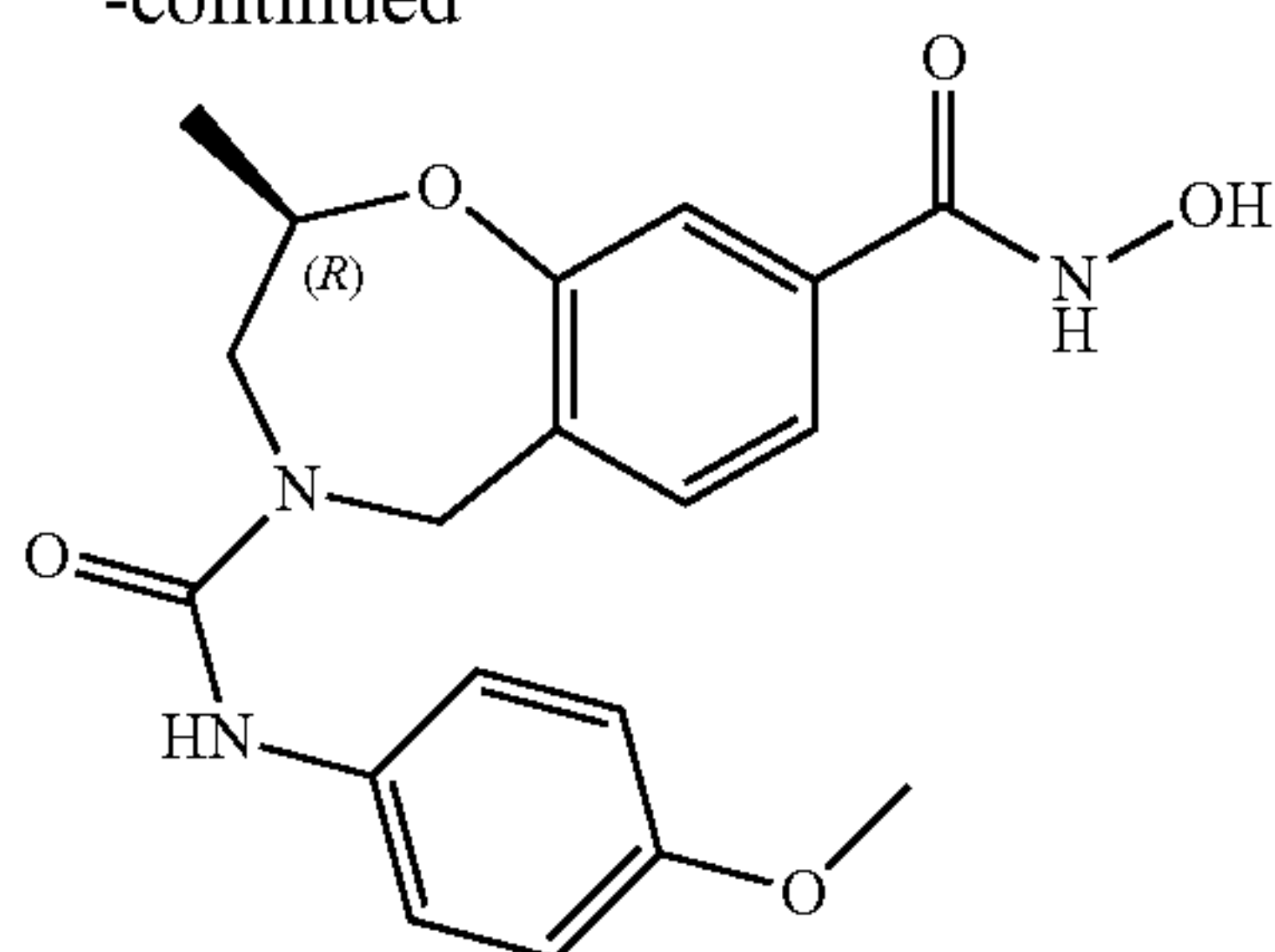
Preparation of (R)—N8-hydroxy-N4-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



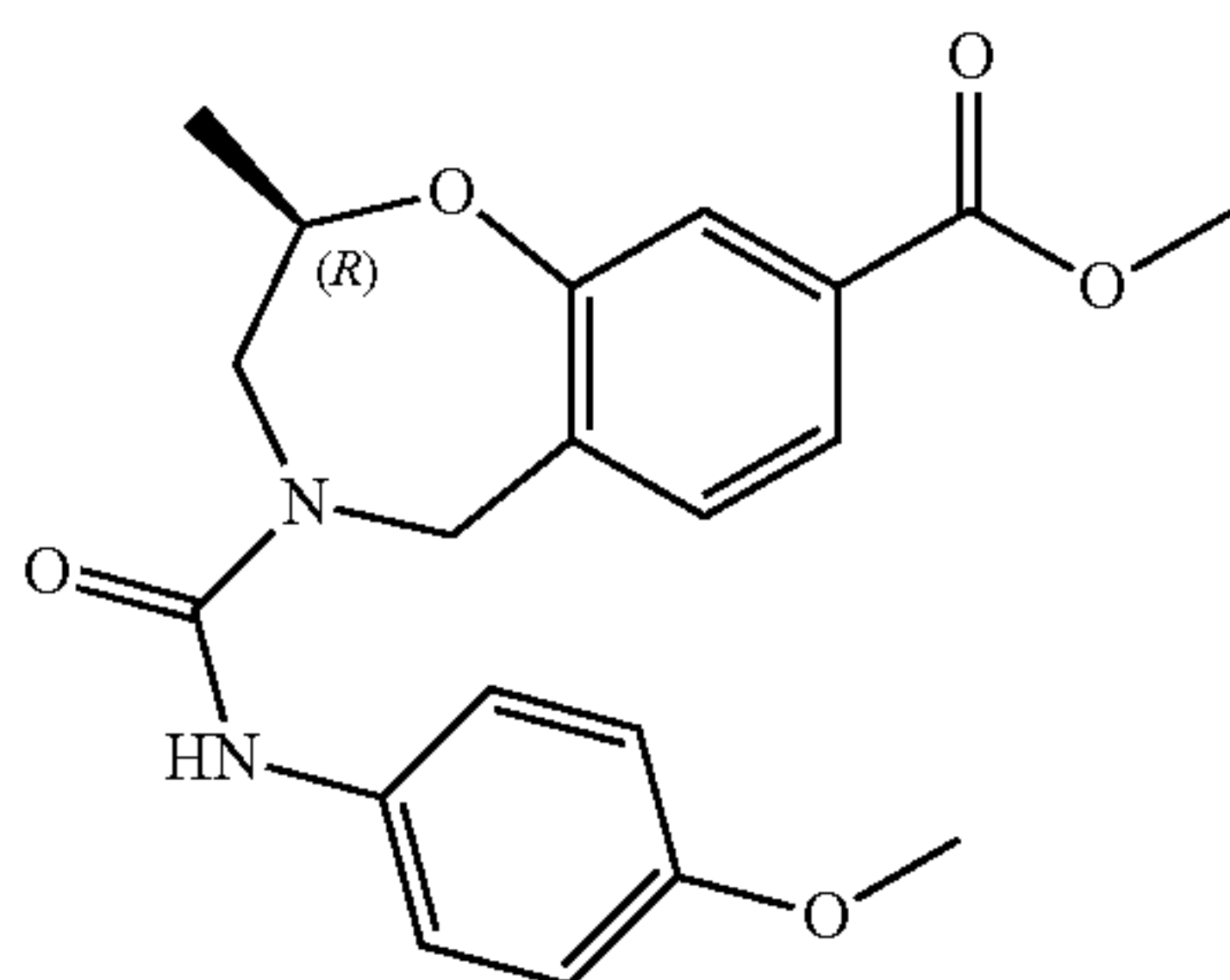


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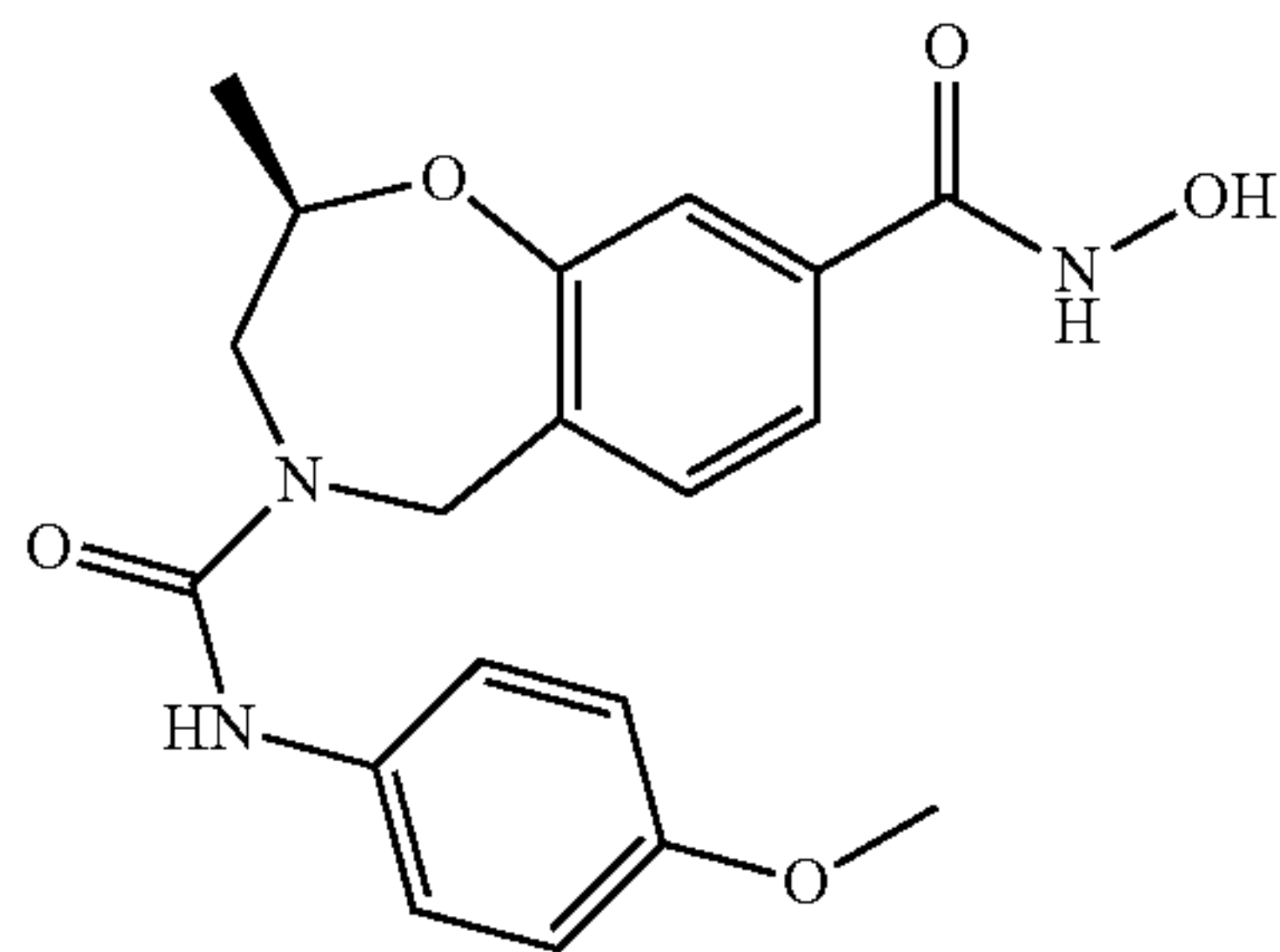


Step-1: Methyl (R)-4-((4-methoxyphenyl)carbamoyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, were placed a solution of methyl (R)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (150 mg, 0.68 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (4 mL),  $\text{Et}_3\text{N}$  (81 mg, 0.80 mmol, 3 equiv) and 1-isocyanato-4-methoxybenzene (167 mg, 1.12 mmol, 1.5 equiv). The resulting mixture was stirred for 16 h at room temperature and then washed with water (2×10 mL). The organic phase was concentrated and the residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a light yellow oil (40 mg, 16% yield). MS: (ES,  $m/z$ ): 371  $[\text{M}+\text{H}]^+$ .

Step-2: (R)—N8-Hydroxy-N4-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8 (5H)-dicarboxamide



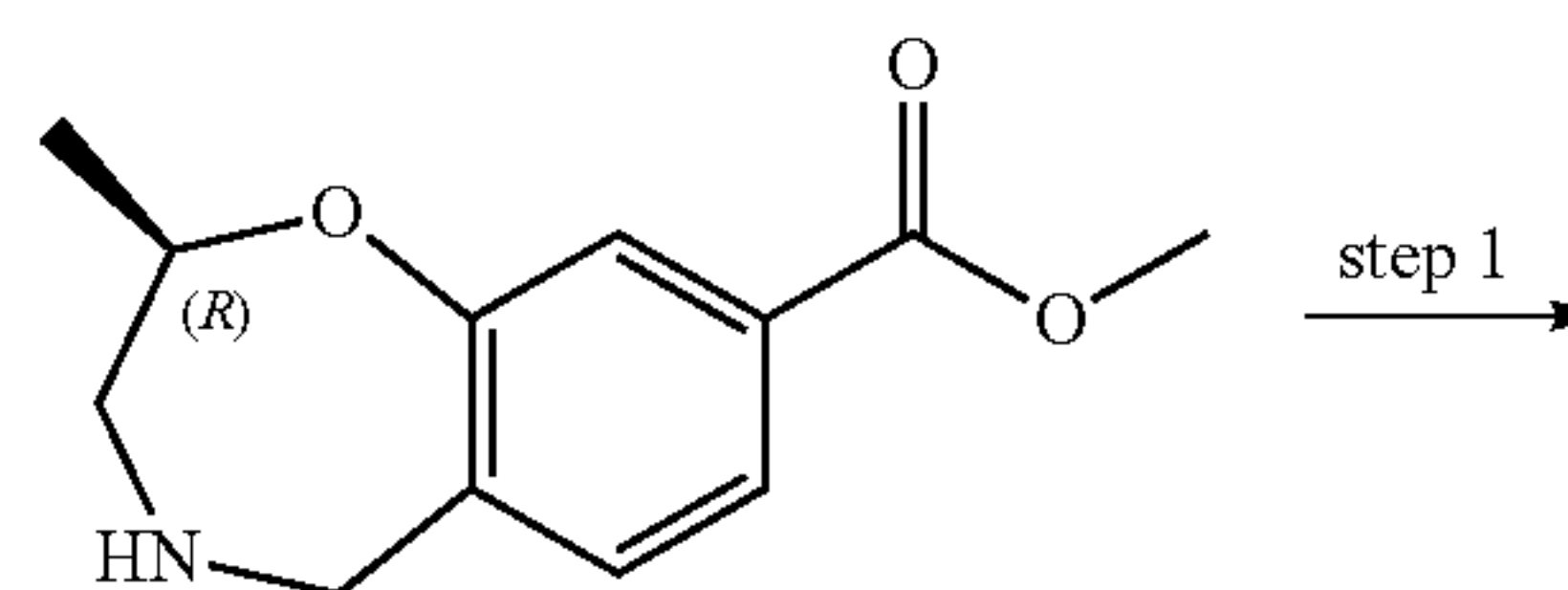
Into a 8-mL vial, was placed methyl (R)-4-((4-methoxyphenyl)carbamoyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (40 mg, 0.11 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL). To this was added aq. 1N NaOH (0.22 mL, 2 equiv) and  $\text{NH}_2\text{OH}$  (50% in water, 0.22 mL, 30 equiv). The resulting solution was stirred for 3 h at room

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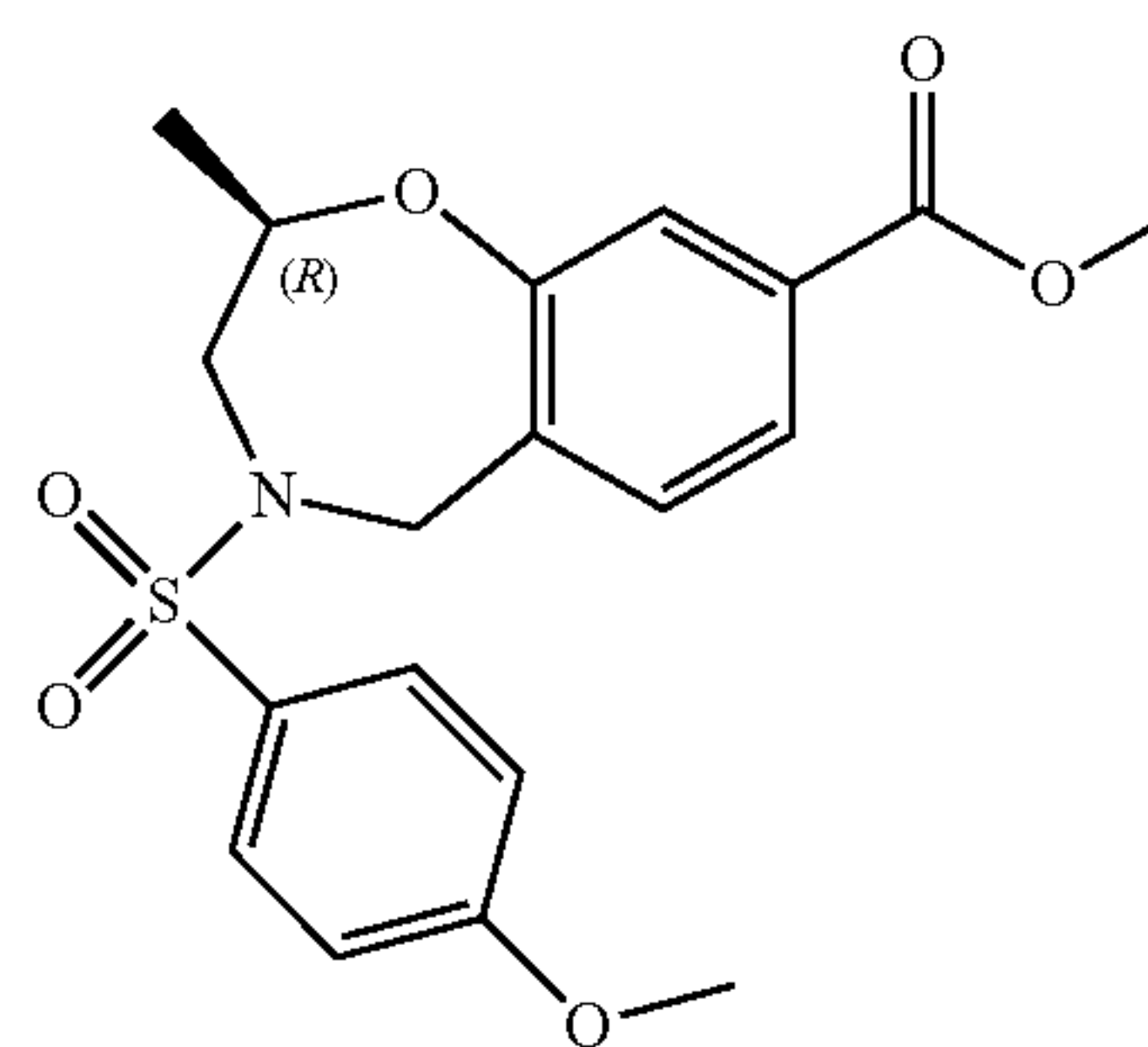
temperature. The crude product was purified by Prep-HPLC (Column: Column: XBridge XP C18 OBD, 5  $\mu\text{m}$ , 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 5% B to 80% B in 7 min; Detector: UV 254, 220 nm) to afford the title compound as an off-white solid (21 mg, 52% yield).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.14 (s, 1H), 9 (br s, 1H), 8.35 (s, 1H), 7.42-7.39 (m, 2H), 7.37-7.33 (m, 1H), 7.27-7.20 (m, 2H), 6.79-7.77 (m, 2H), 4.84-4.80 (d,  $J=15.6$  Hz, 1H), 4.42-4.39 (d,  $J=15.6$  Hz, 1H), 4.03-4 (d,  $J=12.4$  Hz, 2H), 3.67 (s, 3H), 3.32-3.28 (m, 1H), 1.32-1.30 (d,  $J=6.0$  Hz, 3H). MS: (ES,  $m/z$ ): 372  $[\text{M}+\text{H}]^+$ .

## Example 13

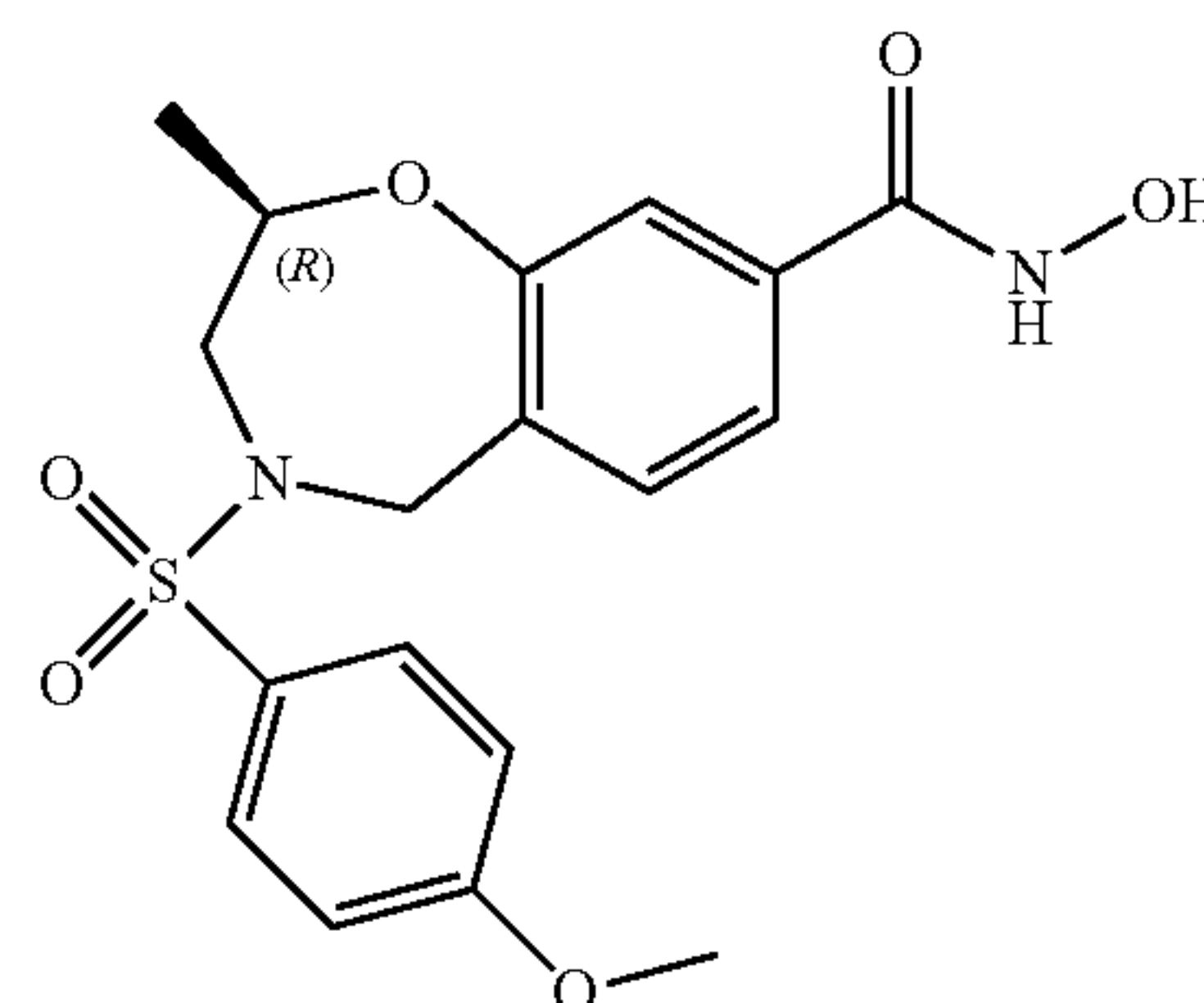
Preparation of (R)—N-Hydroxy-4-(4-methoxyphenylsulfonyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



step 1



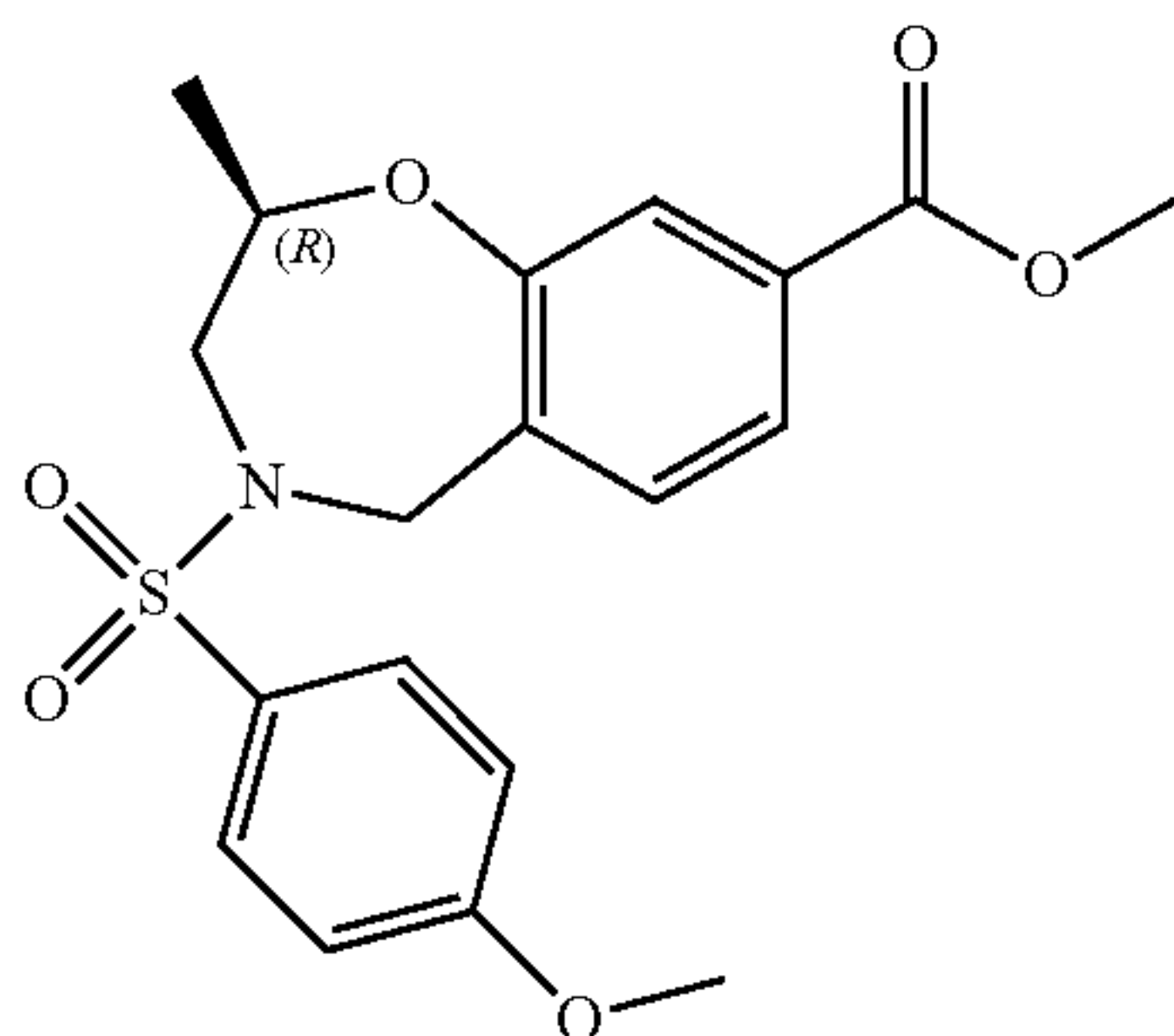
step 2



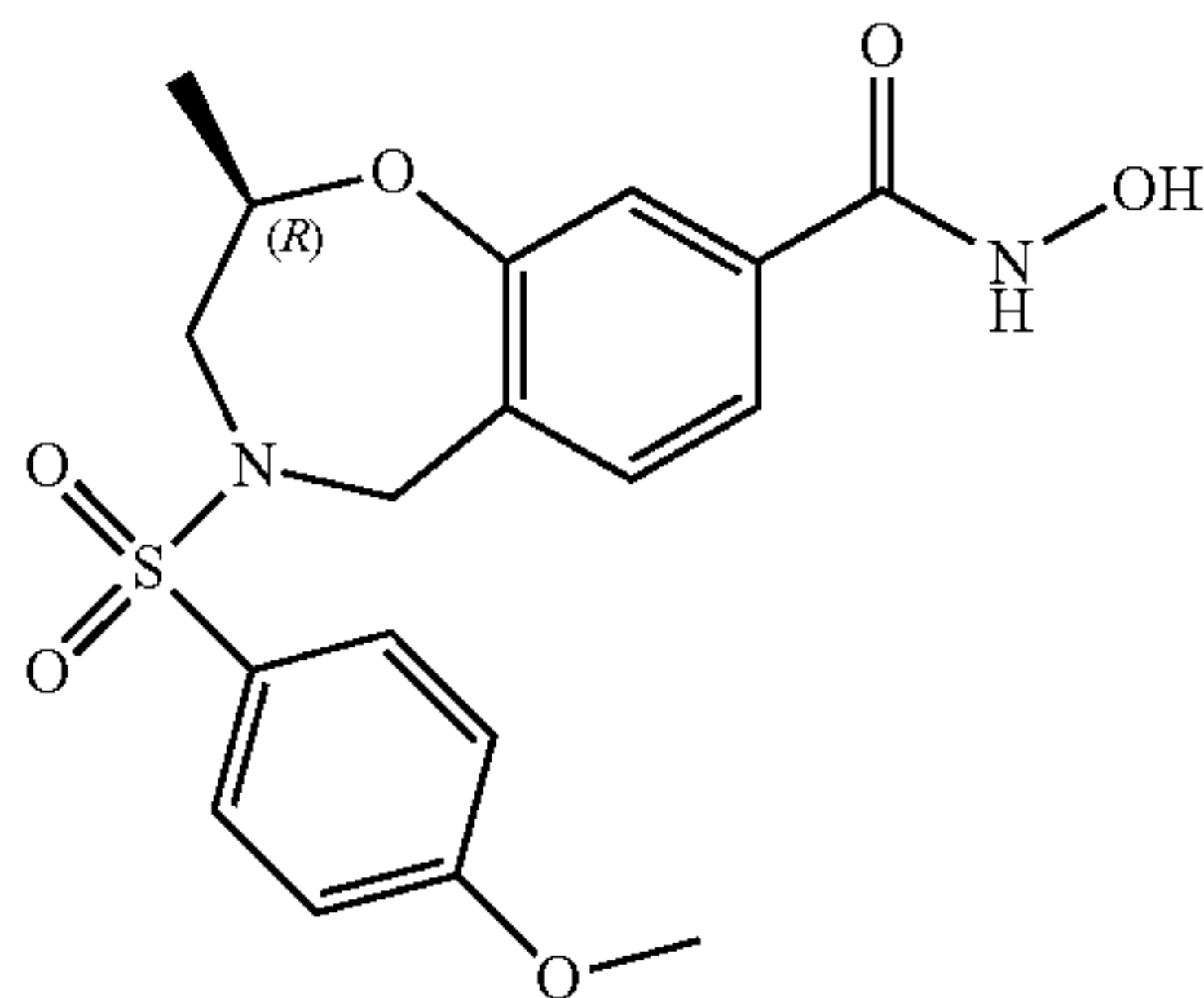


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Step-1: Methyl (R)-4-((4-methoxyphenyl)sulfonyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 40-mL round-bottom flask, was placed a solution of methyl (R)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), 4-methoxybenzene-1-sulfonyl chloride (140 mg, 0.68 mmol, 1.5 equiv), Et<sub>3</sub>N (140 mg, 1.38 mmol, 3 equiv) and 4-dimethylaminopyridine (55 mg, 0.45 mmol, 1 equiv). The resulting mixture was stirred for 10 h at room temperature. The above mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a light yellow oil (80 mg, 45% yield). MS: (ES, m/z): 392 [M+H]<sup>+</sup>. Step-2: (R)-N-Hydroxy-4-((4-methoxyphenyl)sulfonyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

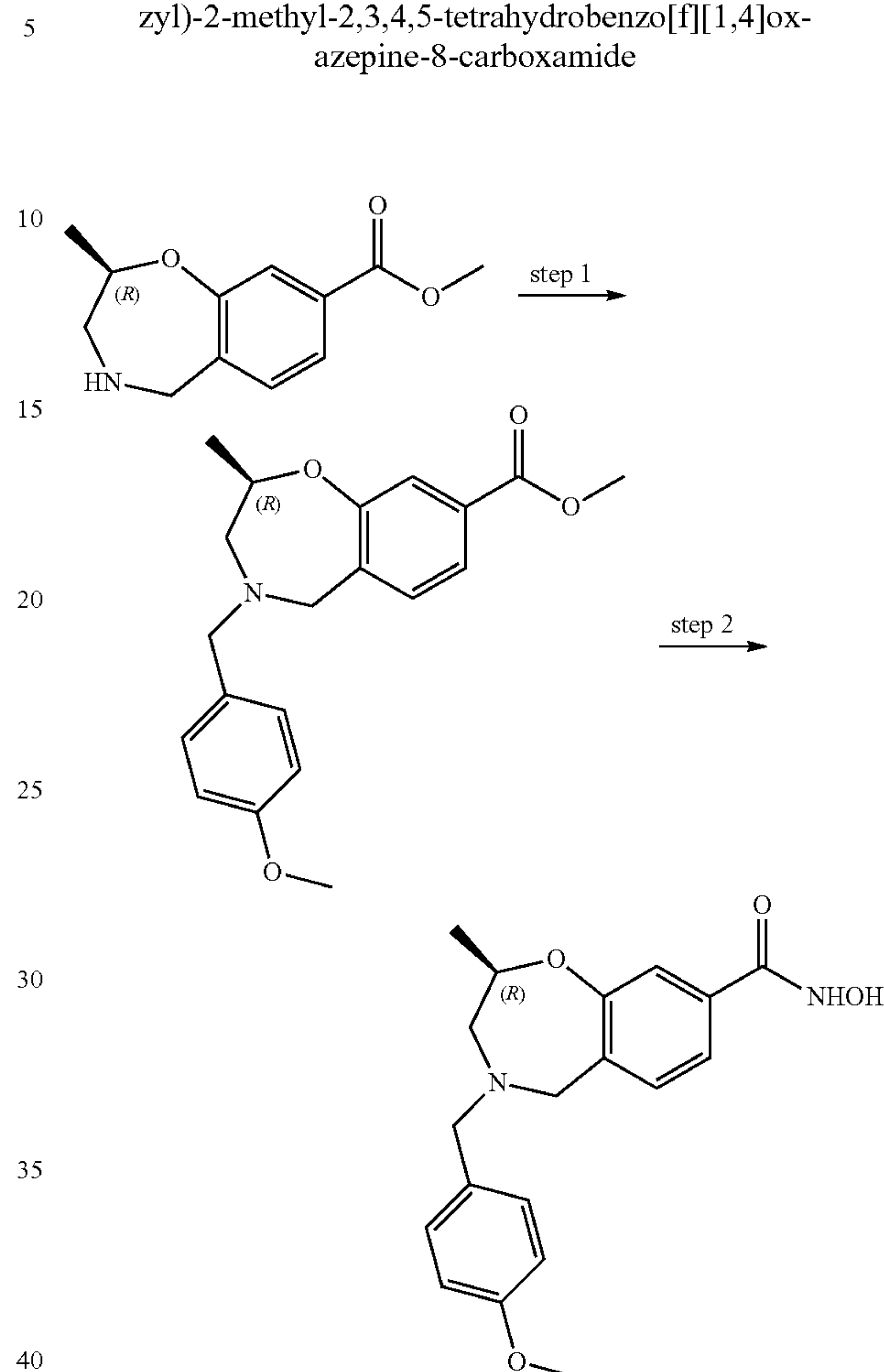


Into a 10-mL vial, was placed a solution of methyl (R)-4-((4-methoxyphenyl)sulfonyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (80 mg, 0.21 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL). This was followed by the addition of aq. 1N NaOH (10.42 mL, 2 equiv) and NH<sub>2</sub>OH (50% in water, 0.42 mL, 30 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge XP C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 8% B to 45% B in 7 min; Detector: UV 254 nm) to afford the title compound as a pink solid (78 mg, 97% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.17 (br s, 1H), 7.69-7.68 (m, 2H), 7.42-7.40 (m, 1H), 7.33-7.31 (m, 1H), 7.25-7.24 (m, 1H), 7.05-7.02 (m, 2H), 4.57-4.53 (m, 1H), 4.25-4.21 (m, 1H), 4.03-3.98 (m, 1H), 3.81 (s, 3H), 3.68-3.65 (m, 1H), 3.24-3.18 (m, 1H), 1.26-1.24 (d, J=6.4 Hz, 3H). MS: (ES, m/z): 393 [M+H]<sup>+</sup>.

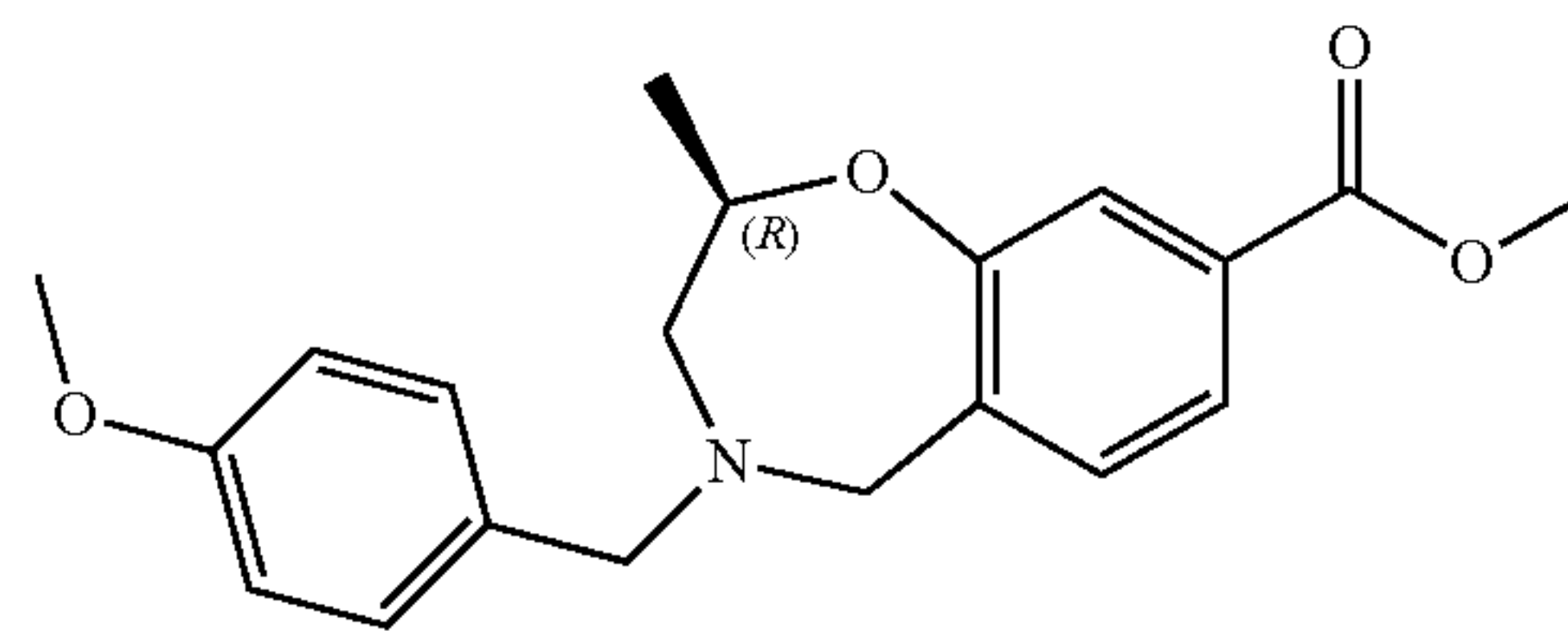
68

Example 14

Preparation of (R)-N-hydroxy-4-(4-methoxybenzyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Step-1: Methyl (R)-4-(4-methoxybenzyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



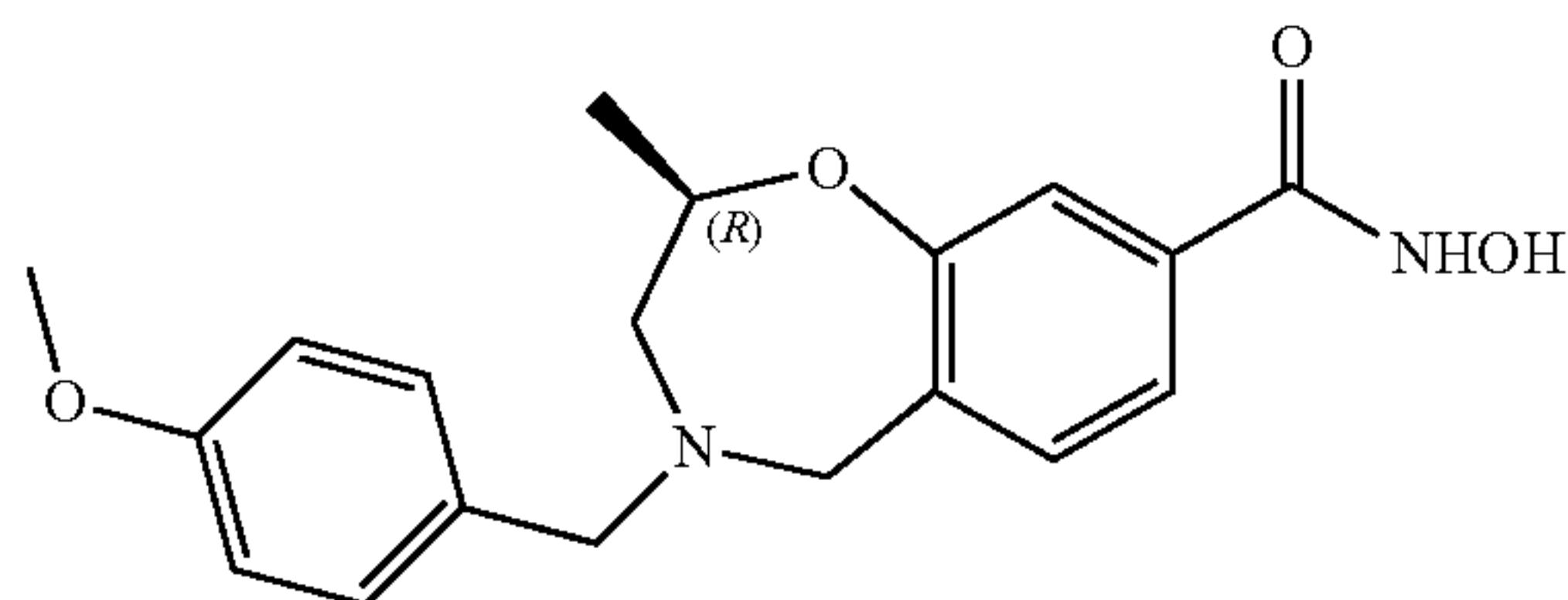
Into a 50-mL flask, was placed a solution of methyl (R)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv) in THF (10 mL). This was followed by the addition of sodium hydride (60%, 50 mg, 2.08 mmol, 3 equiv). To this was added 1-(bromomethyl)-4-methoxybenzene (90 mg, 0.45 mmol, 1 equiv). The resulting mixture was stirred for 4 h at room temperature. The reaction was then quenched by the addition of water (3 mL). The organic layer was concentrated under vacuum to



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afford the title compound as a light yellow oil (80 mg) which was used without further purification. MS: (ES,  $m/z$ ): 342  $[M+H]^+$ .

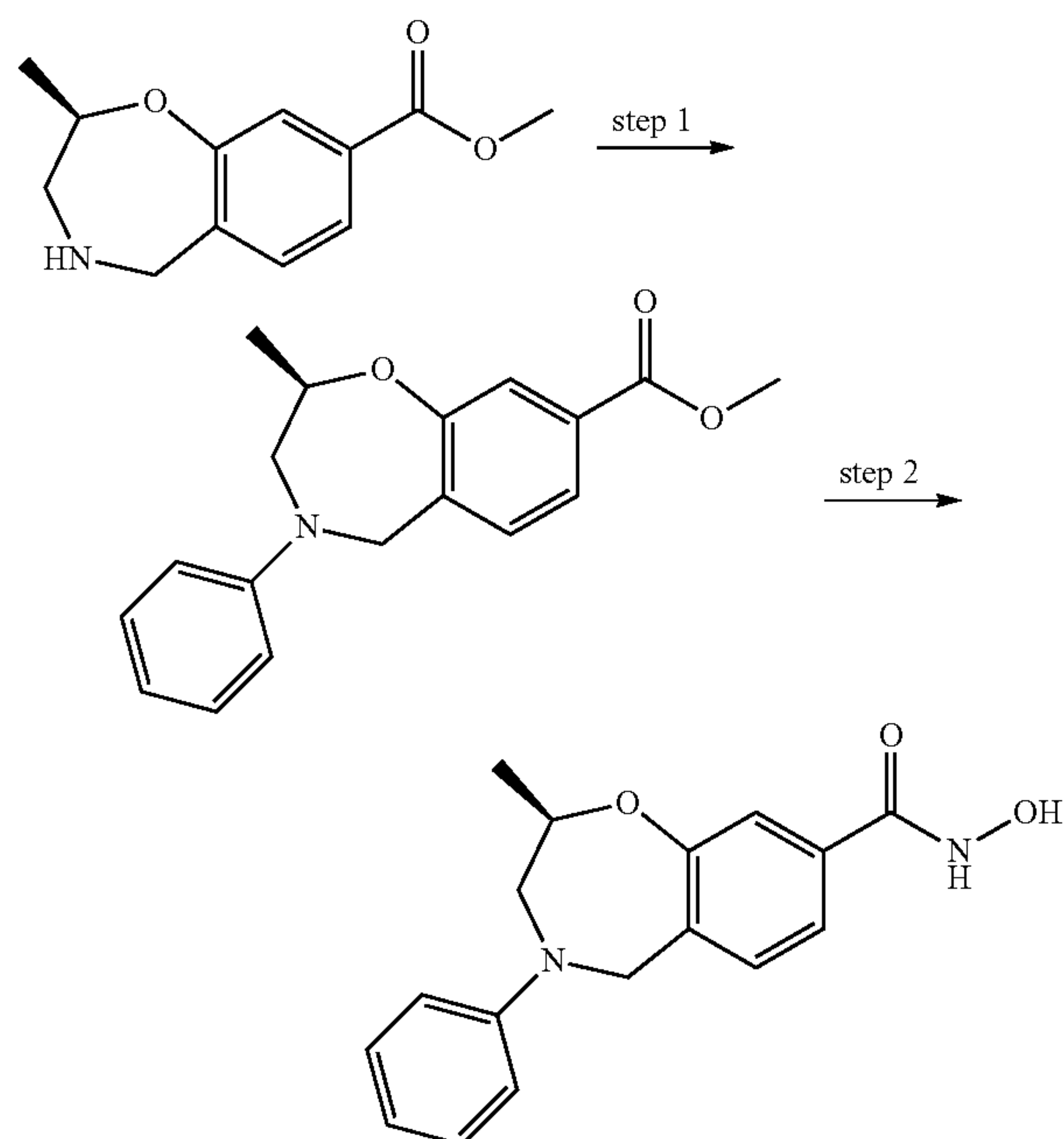
Step-2: (R)—N-Hydroxy-4-(4-methoxybenzyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 10-mL vial, was placed a solution of methyl (R)-4-(4-methoxybenzyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (70 mg, 0.21 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL). To the above mixture was added aq. 1N NaOH (0.42 mL, 2 equiv) and  $NH_2OH$  (50% in water, 0.42 mL, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge XP C18 OBD, 5  $\mu m$ , 19 $\times$ 150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 7% B to 55% B in 7 min; Detector: UV 254 nm) to afford the title compound as a pink solid (34 mg, 49% yield).  $^1H$ -NMR (400 MHz,  $DMSO-d_6$ )  $\delta$ (ppm): 11.30 (br s, 1H), 9.12 (br s, 1H), 7.53-7.44 (m, 5H), 7.03 (m, 2H), 4.49-3.97 (m, 5H), 3.79 (s, 3H), 3.60-3.35 (m, 2H), 1.34-1.33 (d,  $J=5.2$  Hz, 3H). MS: (ES,  $m/z$ ): 343  $[M+H]^+$ .

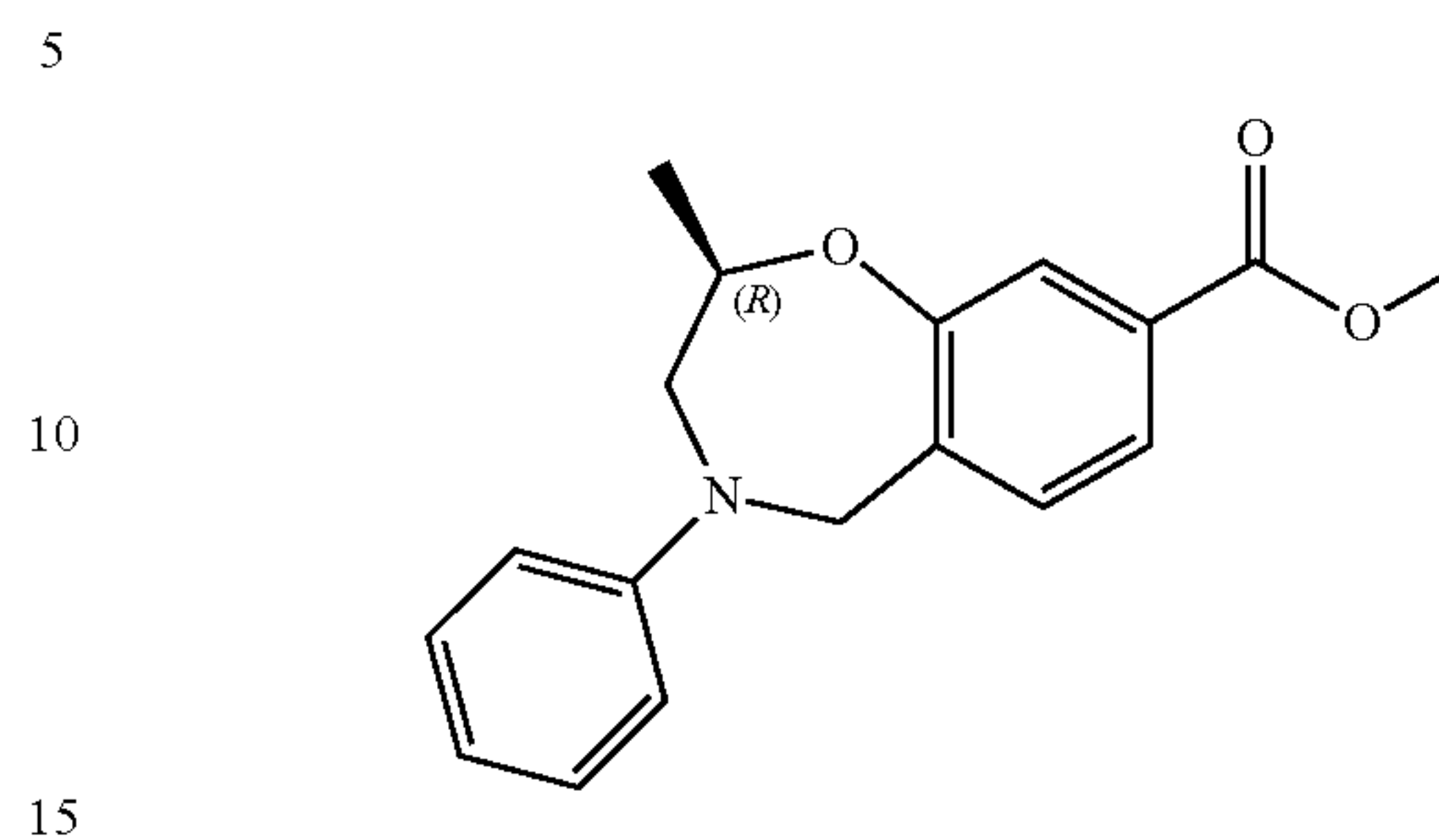
## Example 15

Preparation of (R)—N-hydroxy-2-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



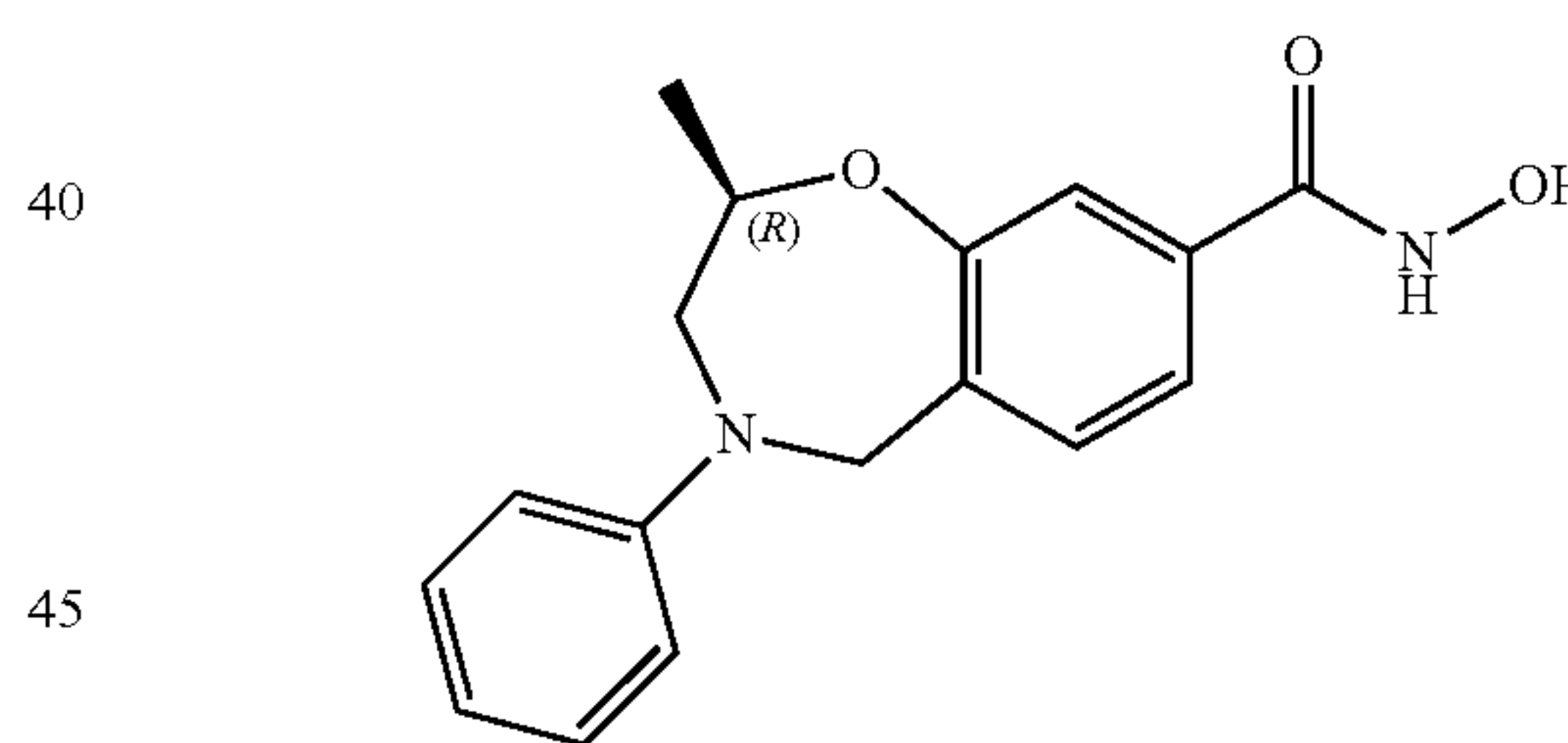
70

Step-1: Methyl (R)-2-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial purged and maintained with nitrogen, placed a solution of methyl (R)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (300 mg, 1.36 mmol, 1 equiv) in dioxane (8 mL), iodobenzene (827 mg, 4.05 mmol, 3 equiv), Xantphos (312 mg, 0.54 mmol, 0.4 equiv),  $Cs_2CO_3$  (1.33 g, 4.05 mmol, 3 equiv) and  $Pd(OAc)_2$  (61 mg, 0.27 mmol, 0.2 equiv). The resulting mixture was stirred for 20 h at 110° C. in an oil bath. The resulting mixture was concentrated under vacuum. The residue was diluted with EtOAc (20 mL), washed with water (3 $\times$ 15 mL), dried and concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a brown oil (270 mg, 67% yield). MS: (ES,  $m/z$ ): 298  $[M+H]^+$ .

Step-2: (R)—N-hydroxy-2-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



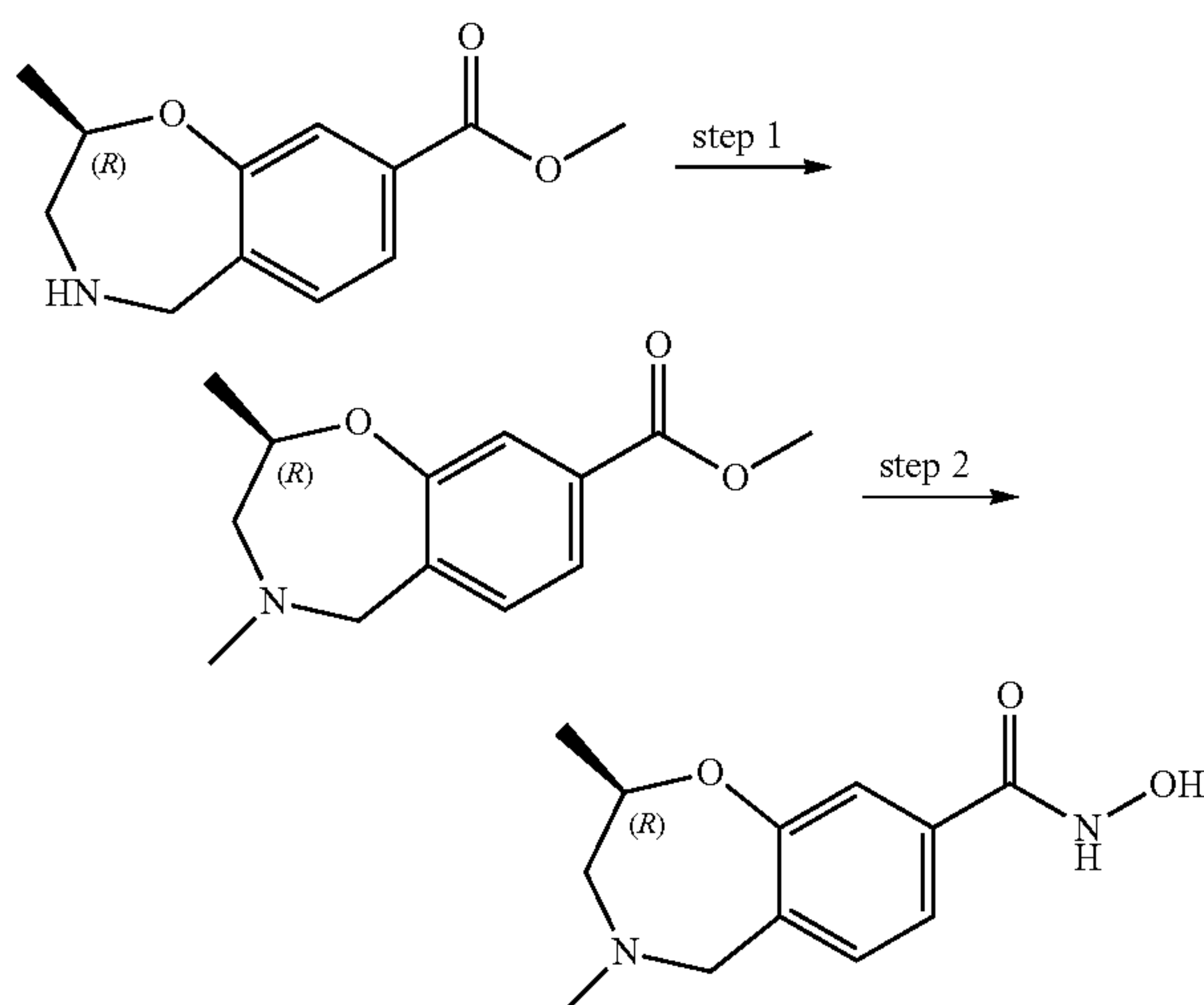
Into a 8-mL vial, was placed methyl (R)-2-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (270 mg, 0.91 mmol, 1 equiv) in THF/MeOH (4:1, 3 mL). To the above mixture was added aq. 1N NaOH (1.82 mL, 1.82 mmol, 2 equiv) and  $NH_2OH$  (50% in water, 1.83 mL, 27.18 mmol, 30 equiv). The resulting mixture was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge XP C18 OBD, 5  $\mu m$ , 19 $\times$ 150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 5% B to 62% B in 7 min; Detector: UV 254 nm) to afford the title compound as a brown solid (134 mg, 49% yield).  $^1H$ -NMR (400 MHz,  $DMSO-d_6$ )  $\delta$ (ppm): 11.29 (br s, 1H), 7.55-7.52 (d,  $J=7.5$  Hz, 1H), 7.37-7.28 (m, 2H), 7.12-7.07 (m, 2H), 6.87-6.84 (m, 2H), 6.59-6.54 (m, 1H), 4.84-4.79 (d,  $J=16.2$  Hz, 1H), 4.48-4.36 (d,  $J=15.6$  Hz, 1H), 4.07-3.87 (m, 3H), 1.37-1.35 (d,  $J=6.3$  Hz, 3H). MS: (ES,  $m/z$ ): 299  $[M+H]^+$ .



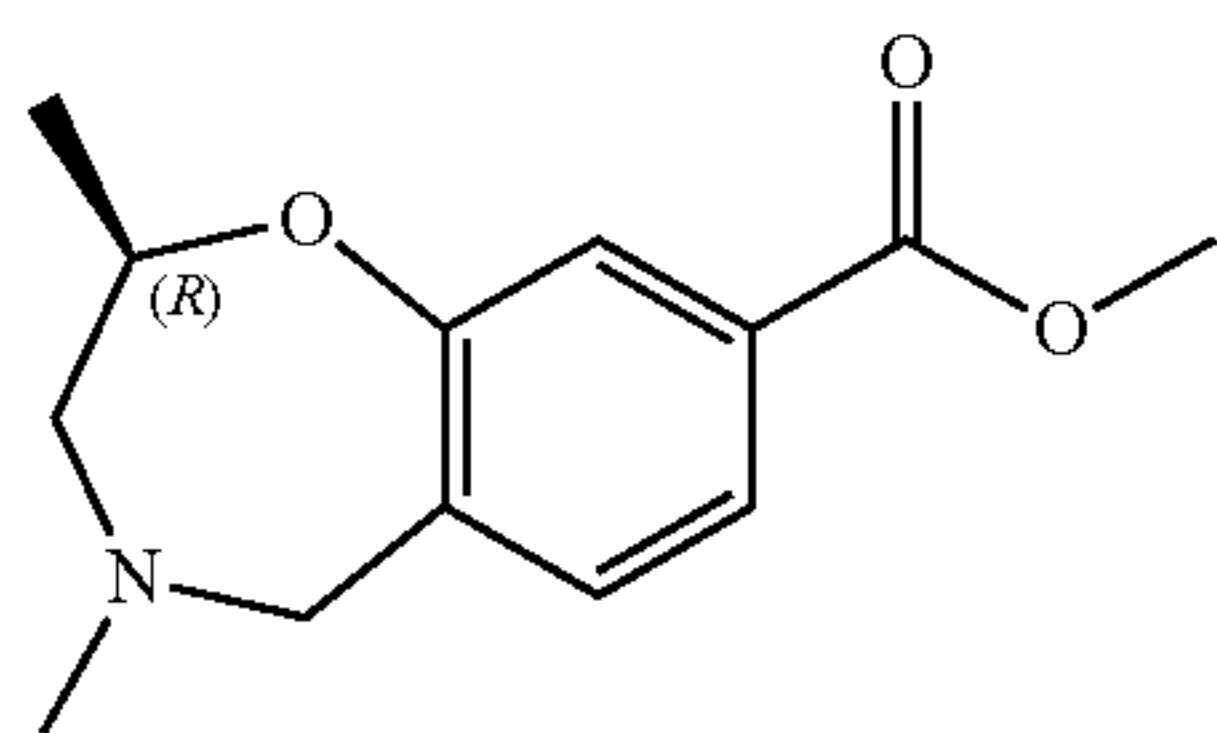
## 71

## Example 16

Preparation of (R)—N-hydroxy-2,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

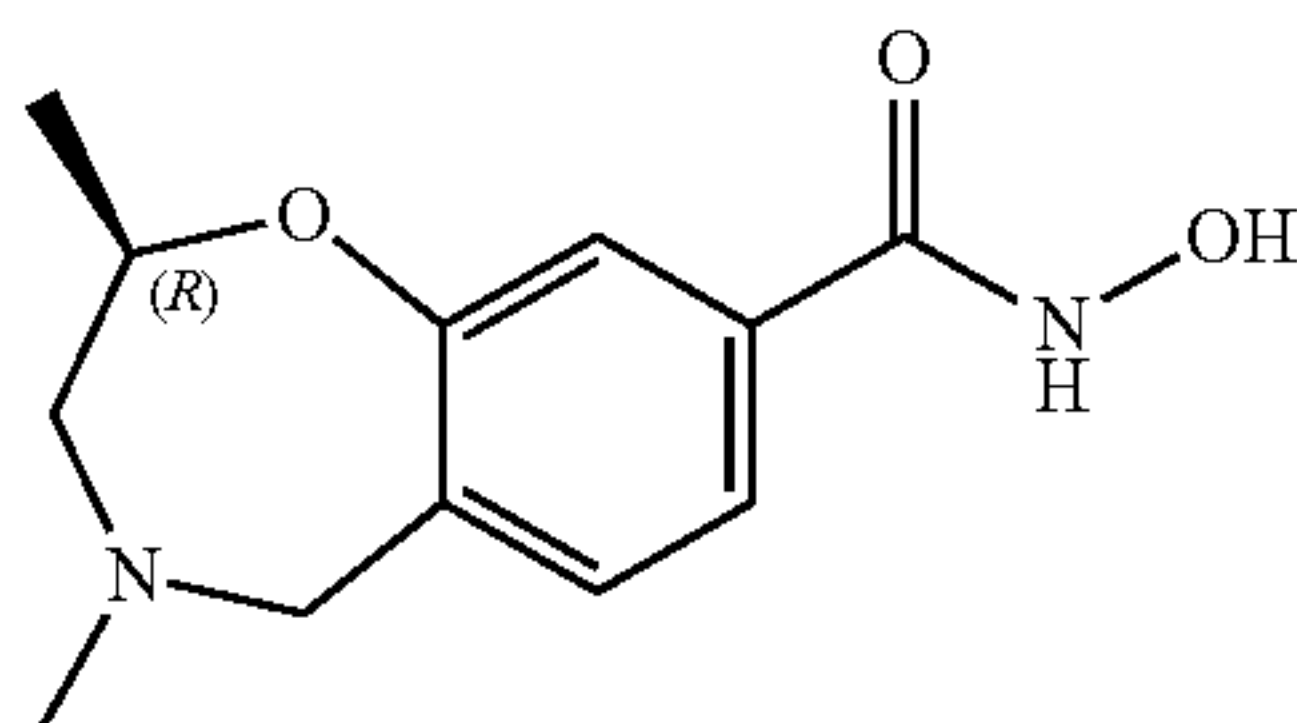


Step-1: Methyl (R)-2,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed a solution of methyl (2R)-2-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxylate (70 mg, 0.32 mmol, 1 equiv) in acetic acid (1.5 mL). This was followed by the addition of formaldehyde (40% in water, 28 mg, 0.93 mmol, 3 equiv) in portions. The mixture was stirred for 2 h at room temperature. To this was added  $\text{NaBH}(\text{OAc})_3$  (334 mg, 1.58 mmol, 5 equiv), in portions at 0° C. The resulting solution was stirred for 18 h at room temperature. The reaction mixture was diluted with EtOAc (40 mL), then washed with water (2×20 mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under vacuum to afford the title compound as a yellow solid (63 mg) which was used without further purification. MS: (ES, m/z): 236  $[\text{M}+\text{H}]^+$ .

Step-2: (R)—N-hydroxy-2,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

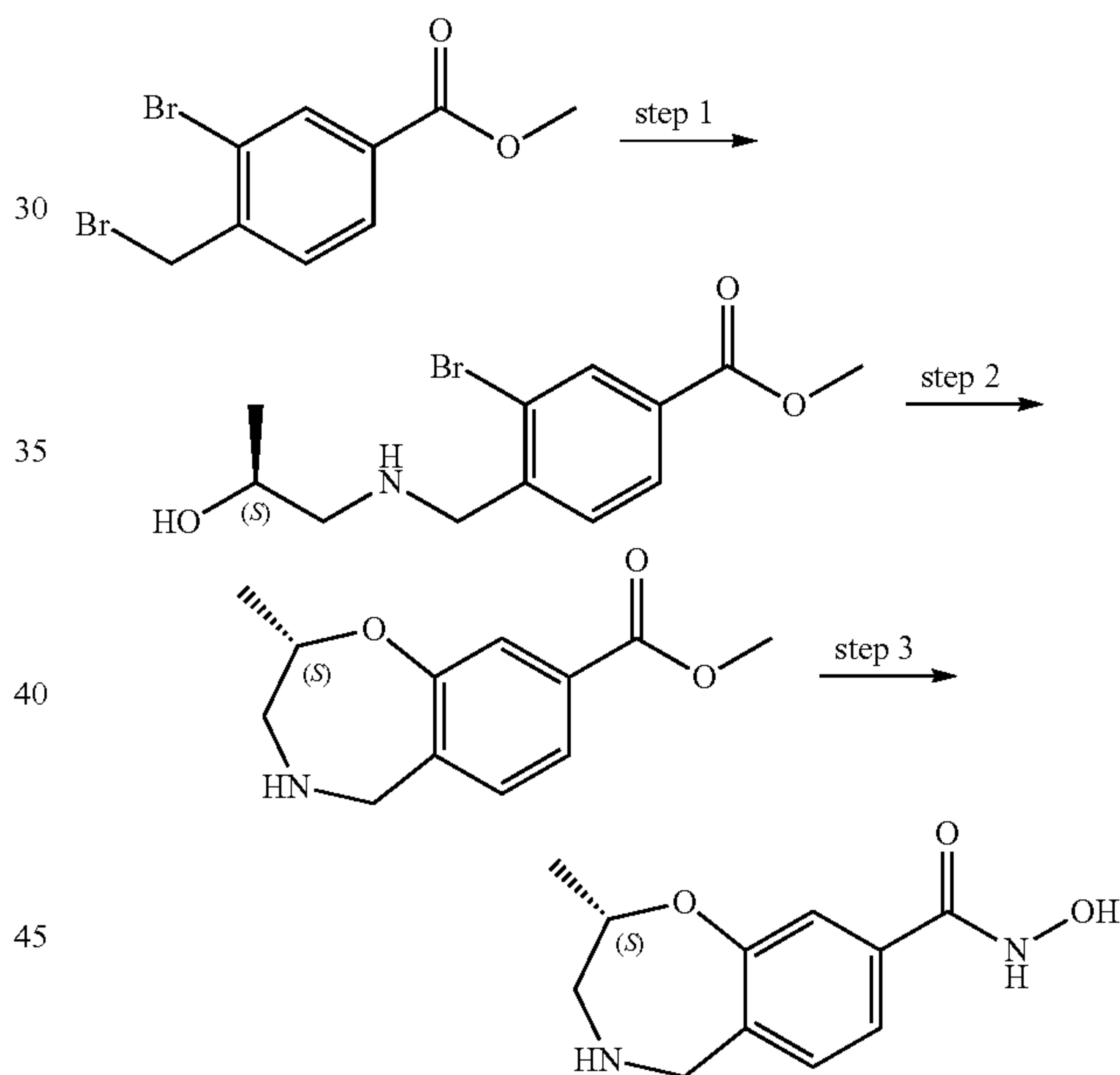


## 72

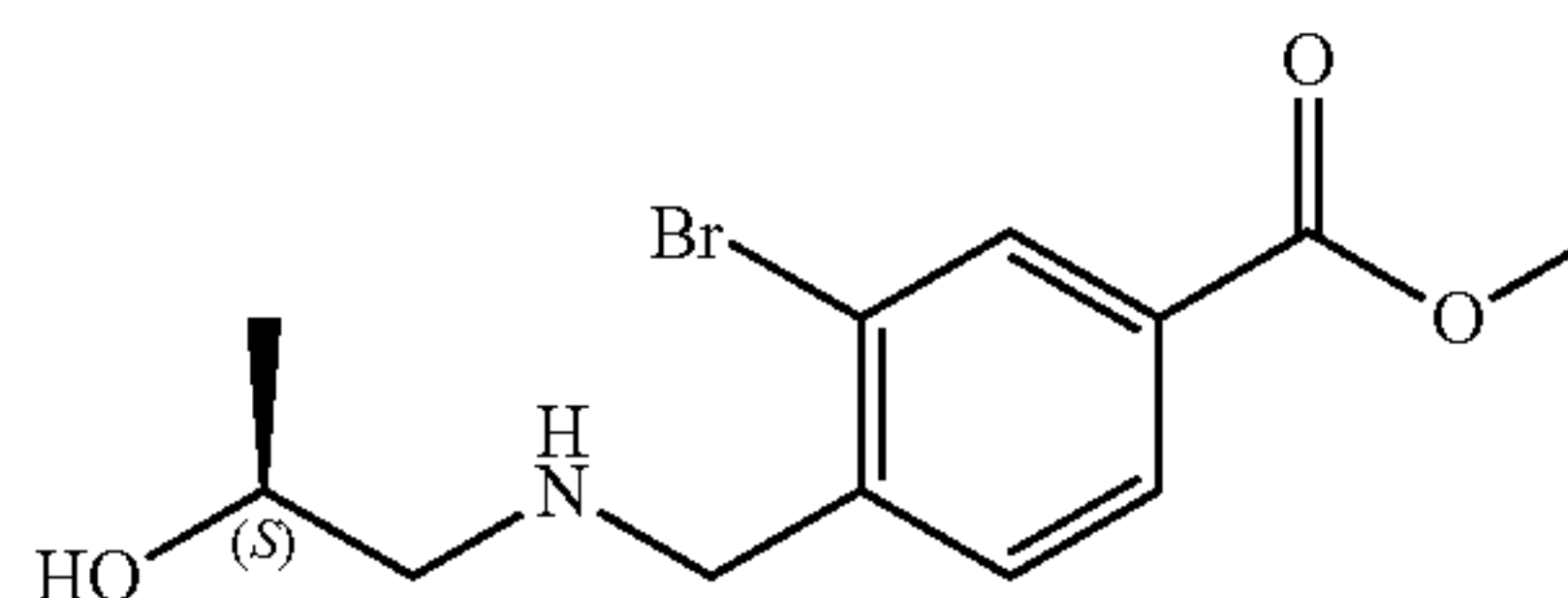
Into a 8-mL vial, was placed a solution of methyl (R)-2,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (134 mg, 0.57 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL). aq. 1N NaOH (1.71 mL, 3 equiv) and  $\text{NH}_2\text{OH}$  (50% in water, 1.13 mL, 30 equiv) were added. The resulting solution was stirred for 15 h at room temperature. The crude product was purified by Prep-HPLC (Column: T3 C18 OBD, 5  $\mu\text{m}$ , 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 3% B to 30% B in 10 min; Detector: UV 254, 220 nm) to afford the title compound as a TFA salt as an off-white solid (5 mg, 4% yield).  $^1\text{H}$ -NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 7.32-7.17 (m, 2H), 7.06-7.01 (s, 1H), 4.56-3.91 (m, 1H), 3.79-3.71 (t, J=17.2 hz, 1H), 3.67-3.51 (t, J=33.2 hz, 1H), 2.89-2.84 (m, 1H), 2.69-2.61 (m, 1H), 2.27-2.25 (d, J=3.6 Hz, 3H), 1.24-1.20 (d, J=8.0 Hz, 3H). MS: (ES, m/z): 237  $[\text{M}+\text{H}]^+$ .

## Example 17

Preparation of (S)—N-hydroxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Step-1: Methyl (S)-3-bromo-4-(((2-hydroxypropyl)amino)methyl)benzoate



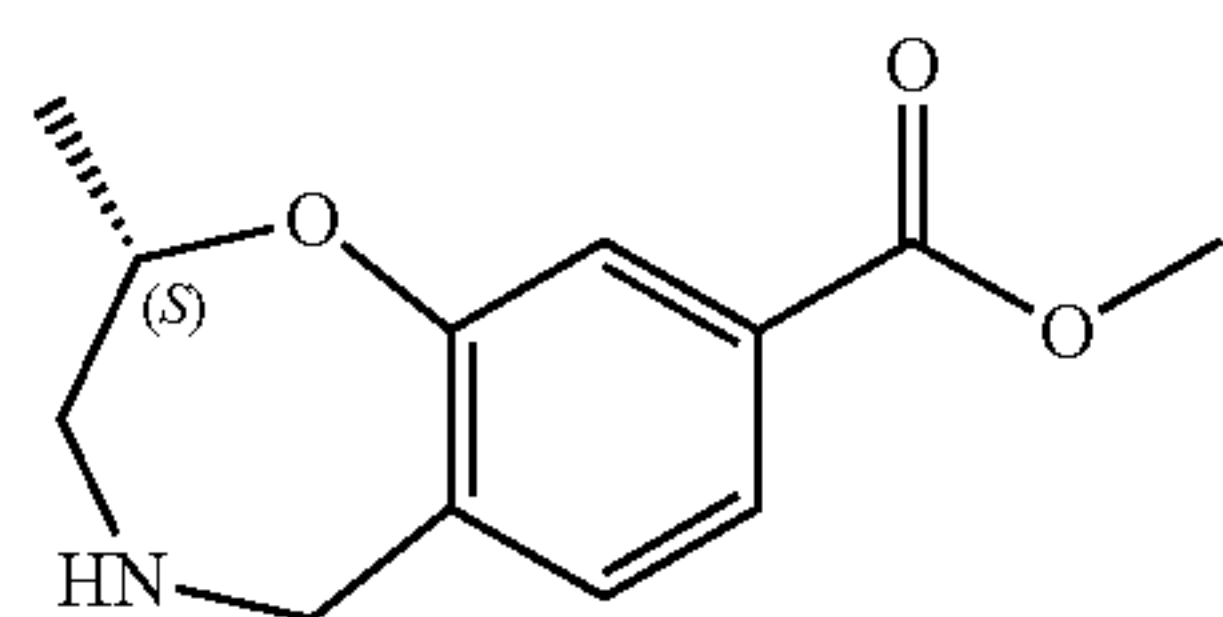
Into a 500-mL round-bottom flask, was placed (2S)-1-aminopropan-2-ol (2.98 g, 39.68 mmol, 1 equiv), MeCN (150 mL) and  $\text{K}_2\text{CO}_3$  (8.24 g, 59.62 mmol, 1.5 equiv). This was followed by the addition of a solution of methyl 3-bromo-4-(bromomethyl)benzoate (12.3 g, 39.94 mmol, 1



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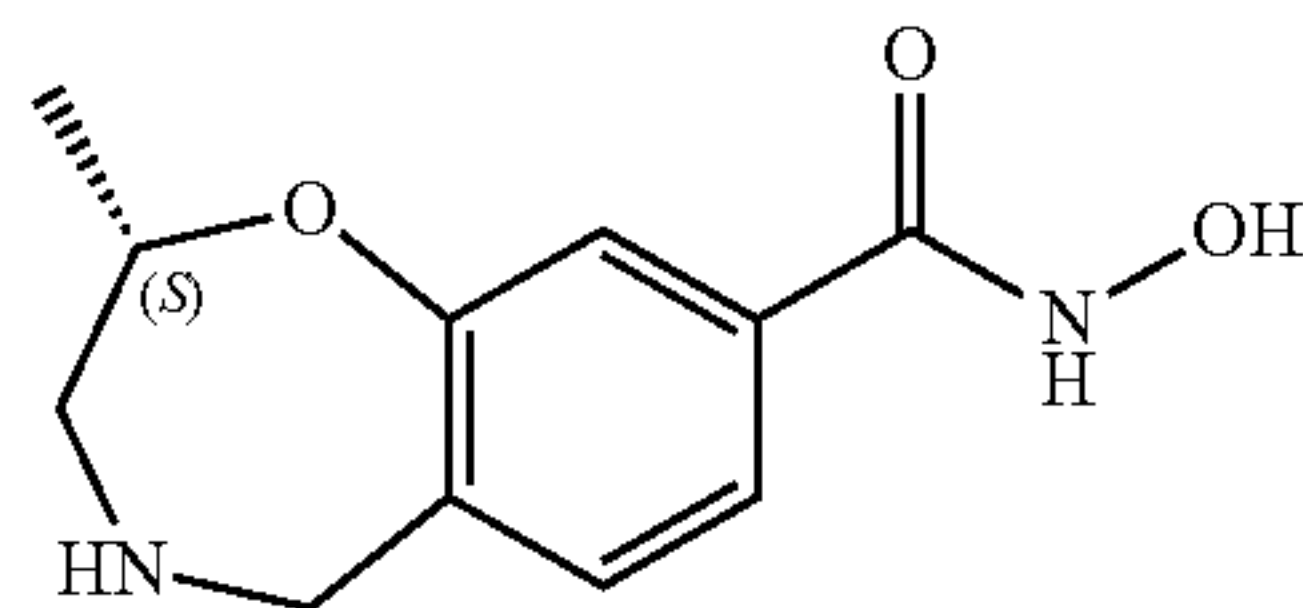
equiv) in MeCN (20 mL) dropwise with stirring at room temperature over 1 h. The resulting solution was stirred for 3 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was diluted with EtOAc (300 mL) and washed with water (3×300 mL). The combined organic layers were dried and concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:5) to afford the title compound as an off-white solid (5.1 g, 42% yield). MS: (ES, m/z): 302 [M+H]<sup>+</sup>.

Step-2: Methyl (S)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 150-mL pressure tank reactor purged and maintained with an inert atmosphere of nitrogen, was placed methyl (S)-3-bromo-4-(((2-hydroxypropyl)amino)methyl)benzoate (5.1 g, 16.88 mmol, 1 equiv), isopropanol (120 mL), K<sub>2</sub>CO<sub>3</sub> (3.510 g, 25.40 mmol, 1.5 equiv) and CuI (966 mg, 5.07 mmol, 0.3 equiv). The resulting solution was stirred for 17 h at 110° C. in an oil bath. The resulting mixture was concentrated under vacuum. The residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with water (2×200 mL), dried and concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:2) to afford the title compound as a yellow oil (2.2 g, 59% yield). <sup>1</sup>H-NMR (DMSO, 400 MHz) δ(ppm): 7.57-7.53 (m, 1H), 7.46-7.44 (m, 1H), 7.30-7.27 (m, 1H), 3.84-3.76 (m, 5H), 3.09-3.05 (d, J=13.6 Hz, 1H), 2.75-2.66 (s, 1H), 1.30-1.29 (d, J=6.4 Hz, 2H), 1.23-1.22 (d, J=6.4 Hz, 3H). MS: (ES, m/z): 222 [M+H]<sup>+</sup>.

Step-3: (S)-N-Hydroxy-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



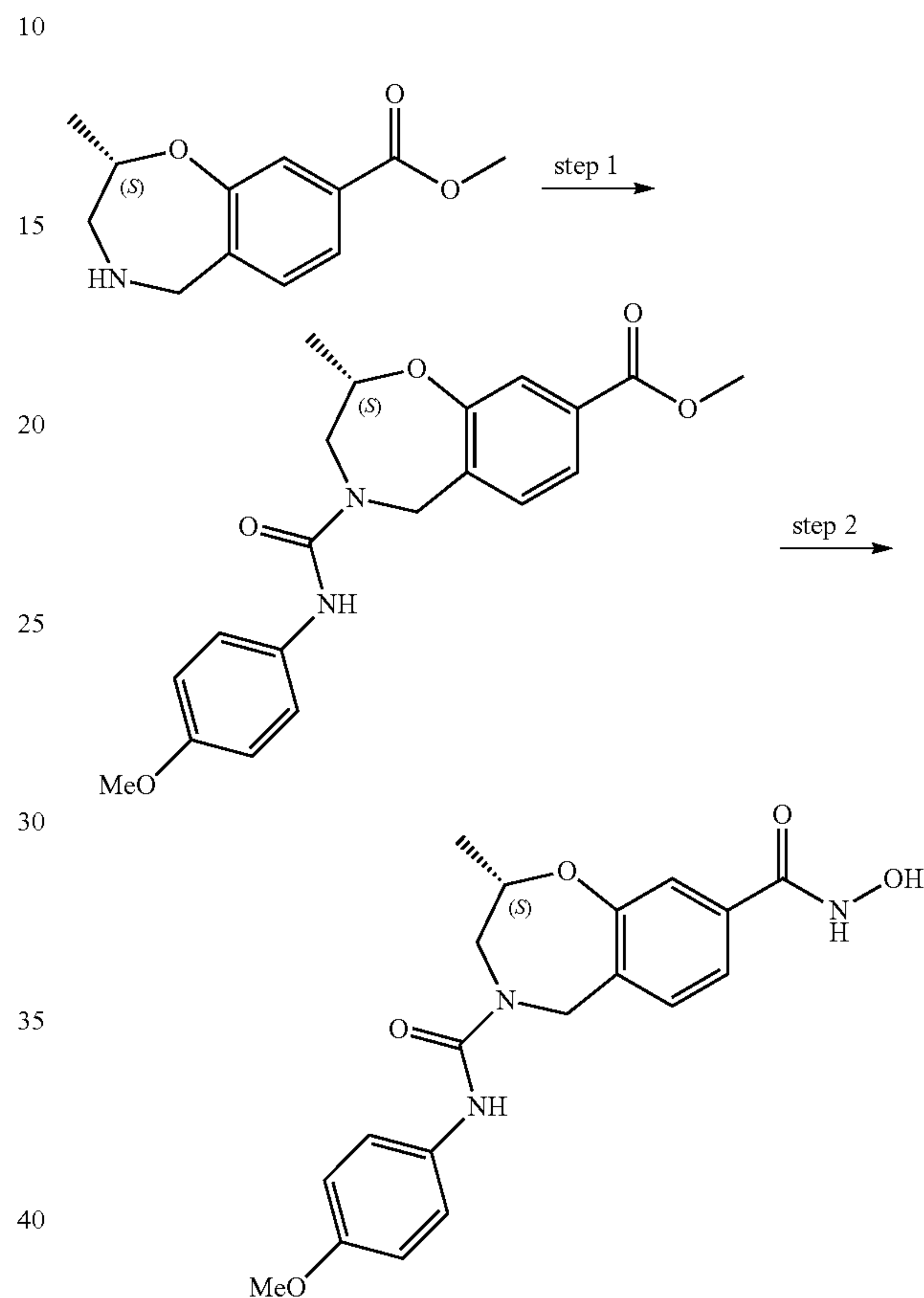
Into a 8-mL vial, was placed a solution of methyl (S)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (50 mg, 0.23 mmol, 1 equiv) in THF/MeOH (4:1, 1 mL), NH<sub>2</sub>OH (50% in water, 0.44 mL, 30 equiv) and aq. 1N NaOH (0.45 mL, 2 equiv) were added. The resulting solution was stirred for 14 h at room temperature. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 4% B to 18% B in 6 min; Detector: UV 254, 220 nm) to afford the title compound as a brown oil (23.5 mg, 31% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.29 (s, 1H), 9.11 (s, 3H), 7.52-7.44 (m, 3H), 4.43-4.39 (d, J=7.2 Hz, 1H), 4.32-4.29 (d, J=7.2 Hz, 1H), 4.19-4.12 (m, 1H),

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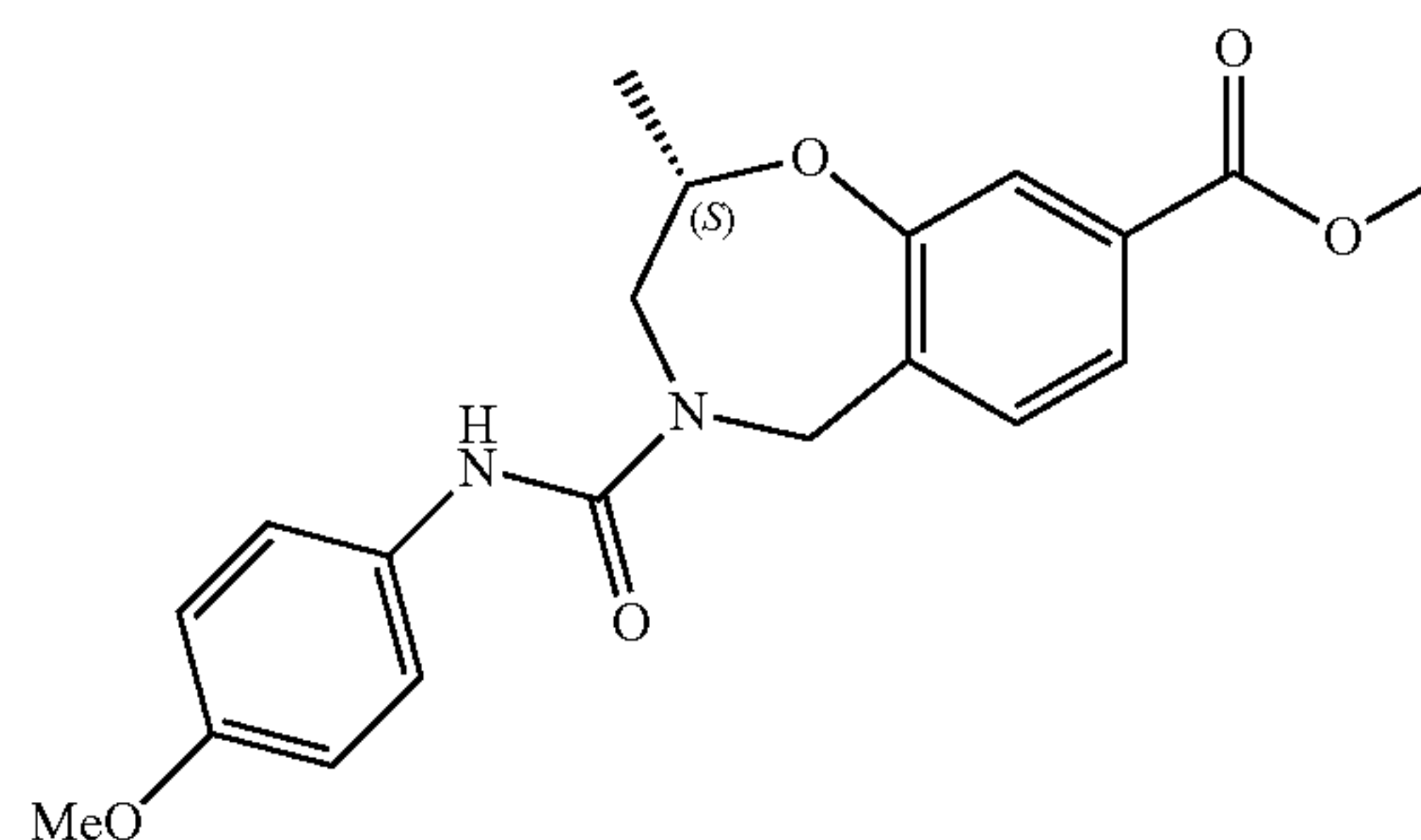
3.53-3.50 (d, J=6.4 Hz, 1H), 3.29-3.25 (d, J=6.8 Hz, 1H), 1.38-1.37 (m, 3H). MS: (ES, m/z): 223 [M+H]<sup>+</sup>.

Example 18

Preparation of (S)-N8-hydroxy-N4-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



Step-1: Methyl (S)-4-((4-methoxyphenyl)carbamoyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



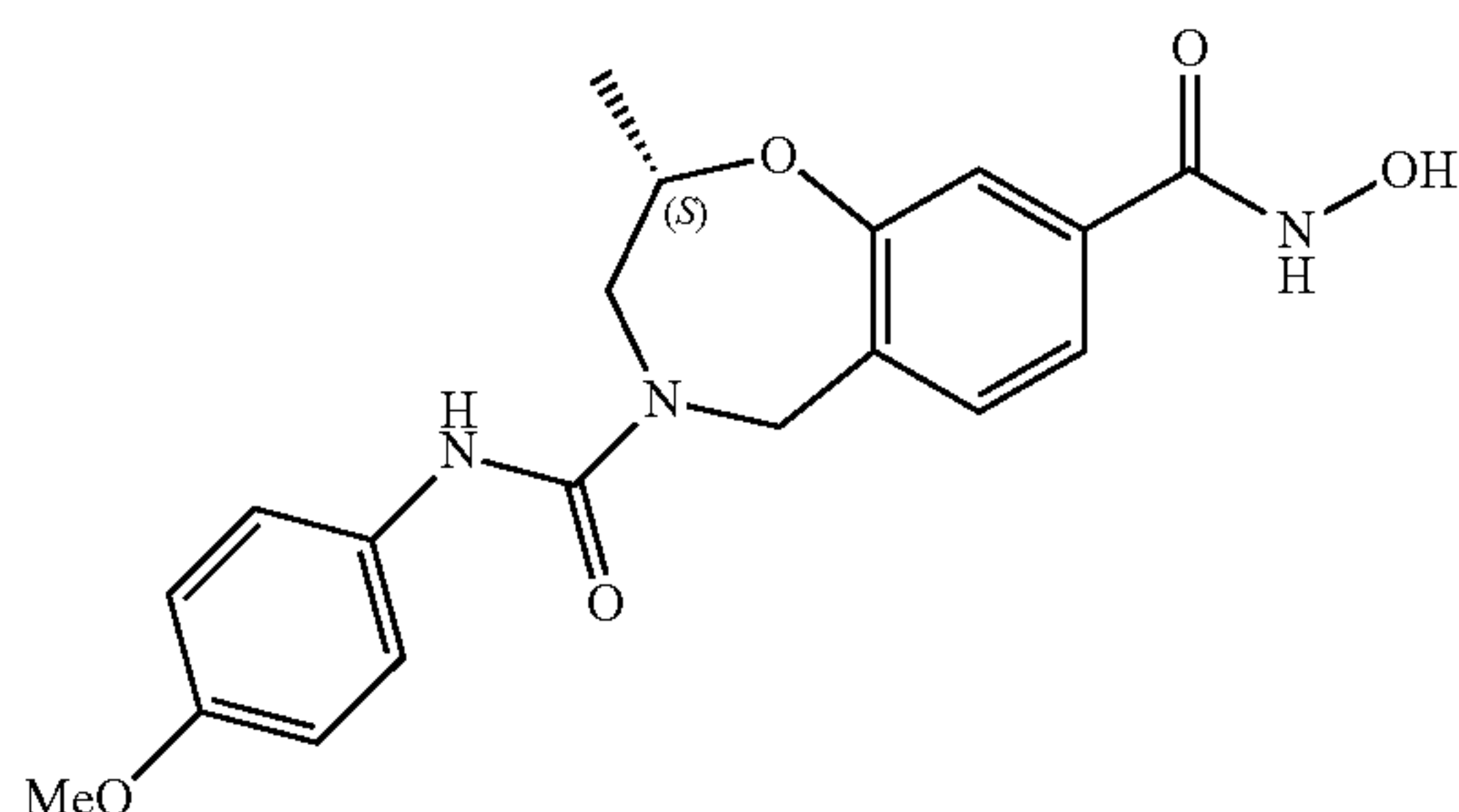
Into a 20-mL vial, was placed a solution of methyl (S)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (150 mg, 0.68 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), 1-isocyanato-4-methoxybenzene (150 mg, 1.01 mmol, 1.2 equiv) and Et<sub>3</sub>N (0.18 mg, 3 equiv). The resulting



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solution was stirred for 10 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a light yellow oil (150 mg, 60% yield). MS: (ES, m/z): 371 [M+H]<sup>+</sup>.

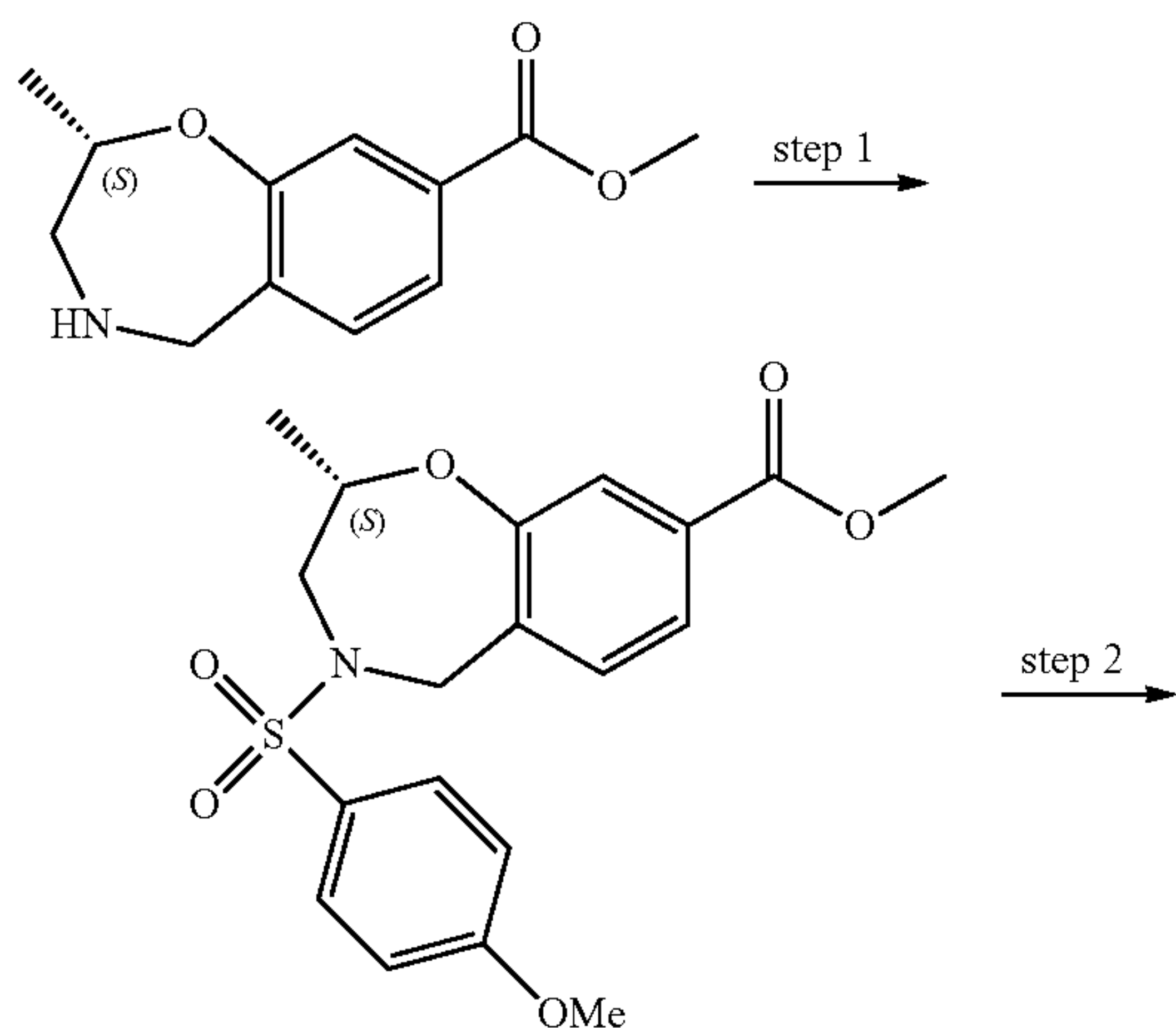
Step-2: (S)—N8-Hydroxy-N4-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



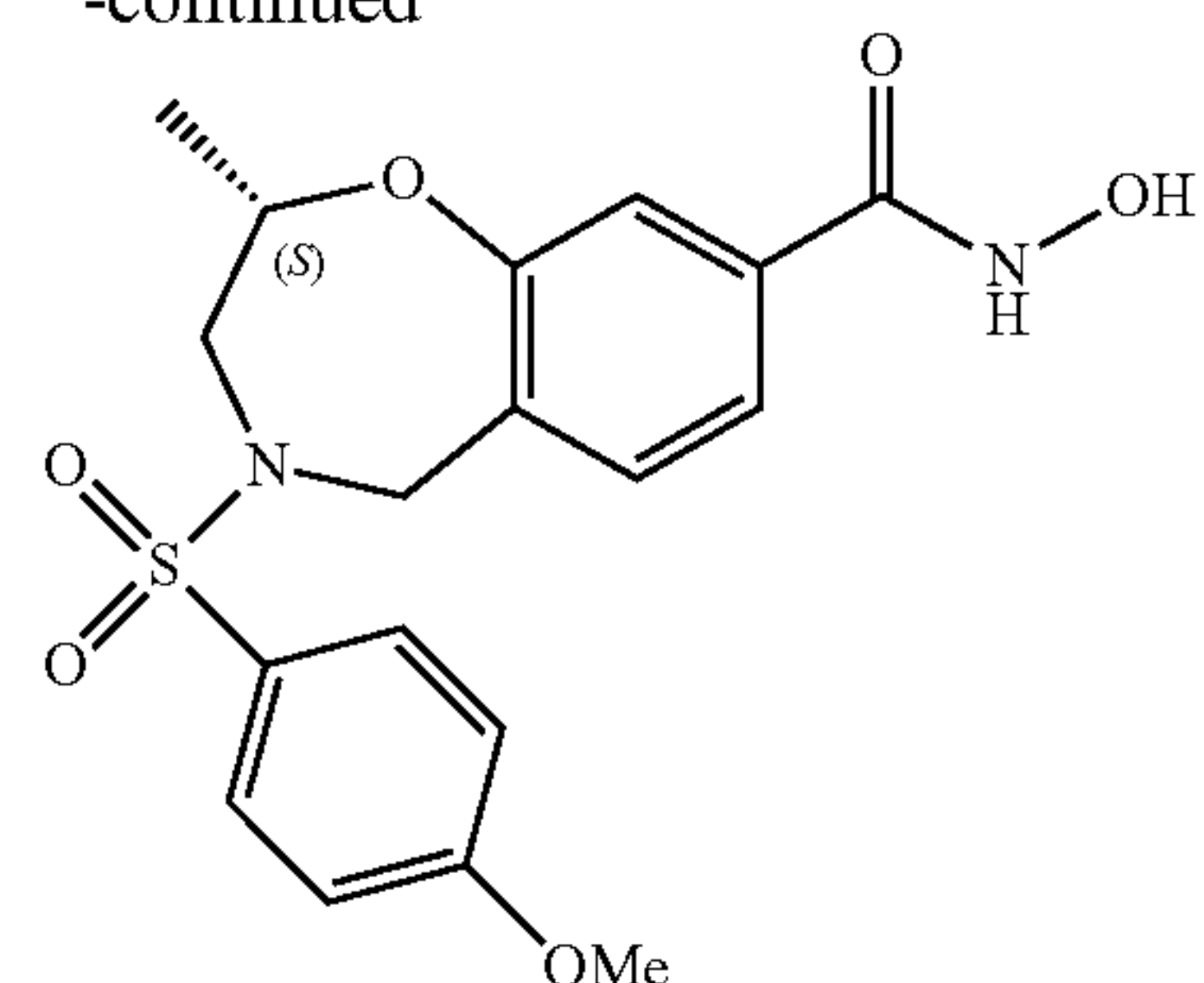
Into a 10-mL vial, was placed a solution of methyl (S)-4-((4-methoxyphenyl)carbamoyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (370 mg, 1 mmol, 1 equiv) in THF/MeOH (4:1, 4 mL). This was followed by the addition of aq. 1N NaOH (1 mL, 2 equiv). To this was added NH<sub>2</sub>OH (50% in water, 1 mL, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge XP C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 10% B to 60% B in 7 min; Detector: UV 254 nm) to afford the title compound as a light brown solid (106 mg, 73% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.14 (br s, 1H), 8.36 (br s, 1H), 7.43-7.38 (m, 2H), 7.28-7.24 (m, 2H), 6.81-6.80 (m, 2H), 4.85-4.81 (d, J=15.6 Hz, 1H), 4.43-4.39 (d, J=15.6 Hz, 1H), 4.04-4.01 (d, J=12.8 Hz, 1H), 3.76 (s, 3H), 3.43-3.37 (m, 2H), 1.32-1.31 (d, J=6.4 Hz, 3H). MS: (ES, m/z): 372 [M+H]<sup>+</sup>.

#### Example 19

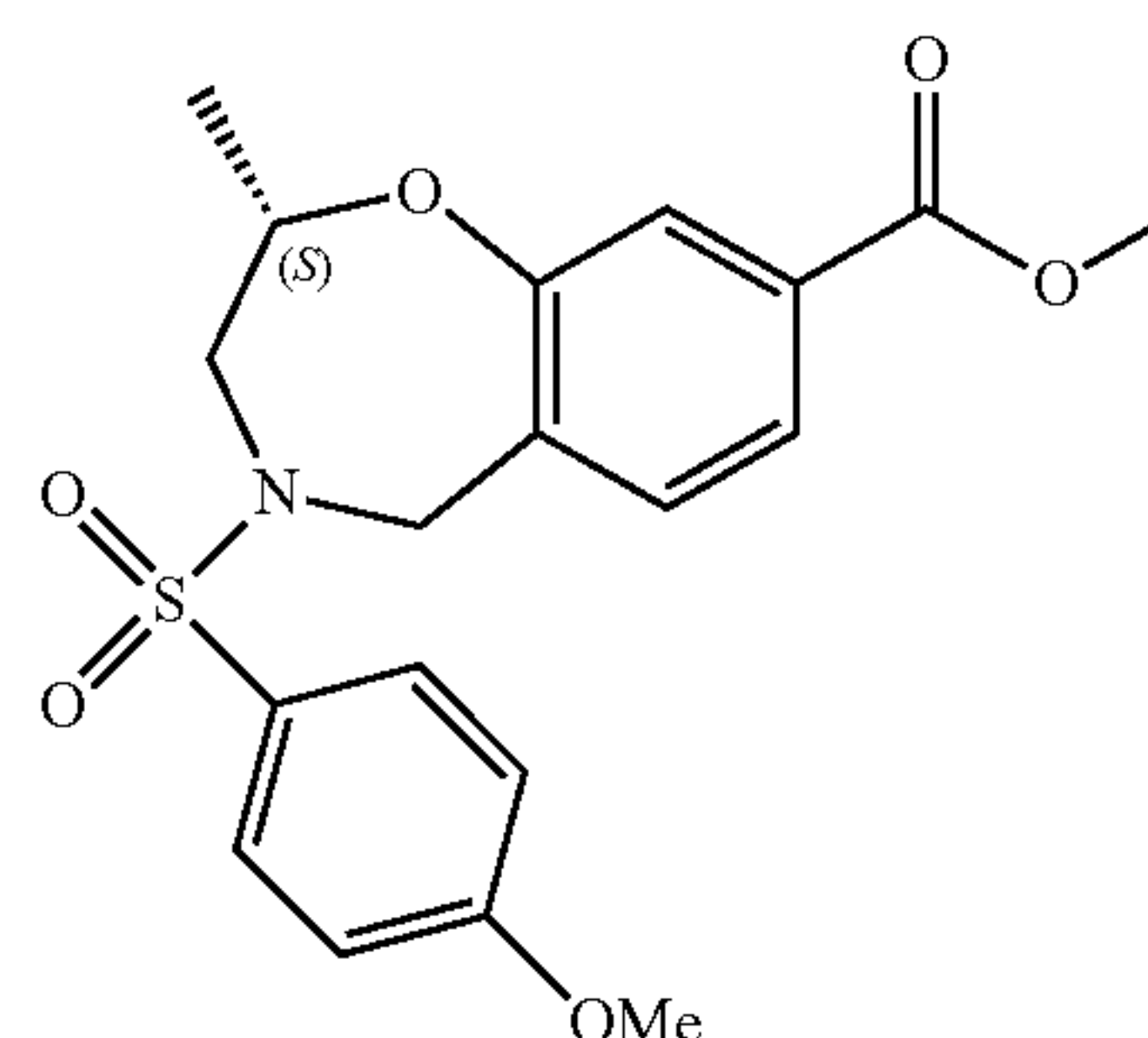
Preparation of (S)—N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

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-continued

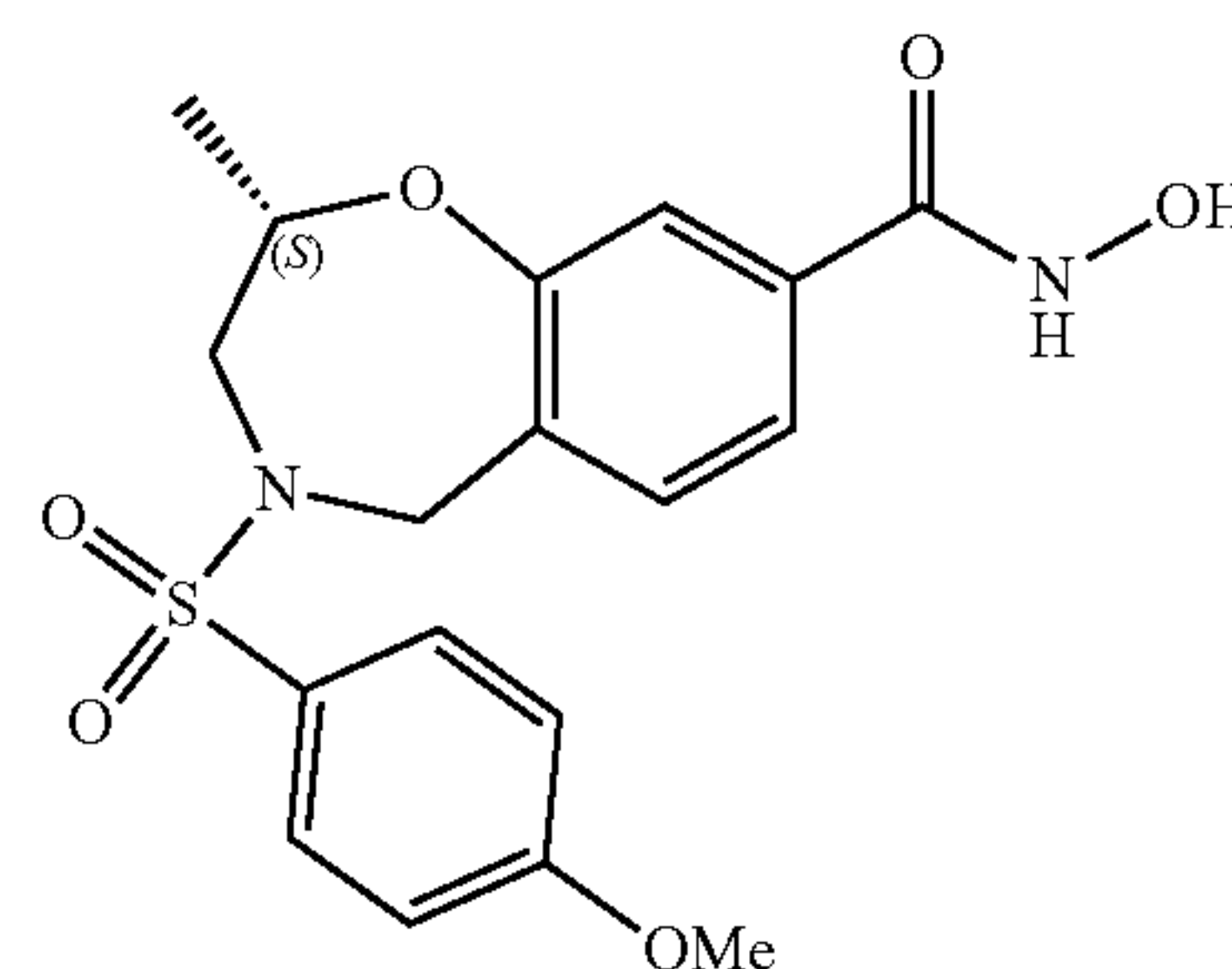


Step-1: Methyl (S)-4-((4-methoxyphenyl)sulfonyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 50-mL flask, was placed a solution of methyl (S)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), Et<sub>3</sub>N (140 mg, 1.38 mmol, 3 equiv) and 4-dimethylaminopyridine (55 mg, 0.45 mmol, 1 equiv), then 4-methoxybenzene-1-sulfonyl chloride (140 mg, 0.68 mmol, 1.5 equiv) was added at 0° C. The resulting solution was stirred for 4 h at room temperature and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a yellow solid (80 mg, 45% yield). MS: (ES, m/z): 392 [M+H]<sup>+</sup>.

Step-2: (S)—N-Hydroxy-4-((4-methoxyphenyl)sulfonyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 10-mL vial, was placed a solution of methyl (S)-4-((4-methoxyphenyl)sulfonyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (80 mg, 0.20

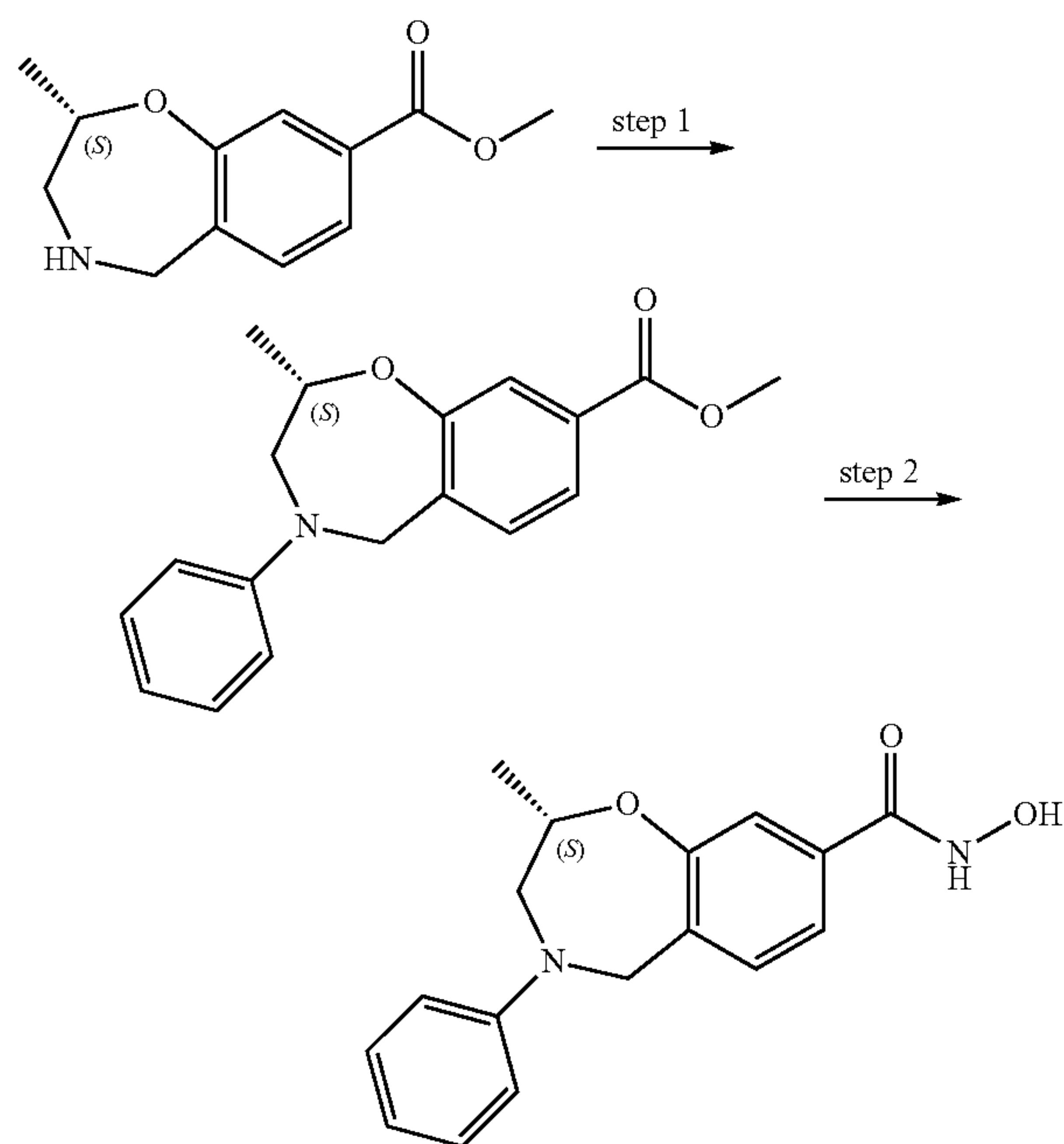


77

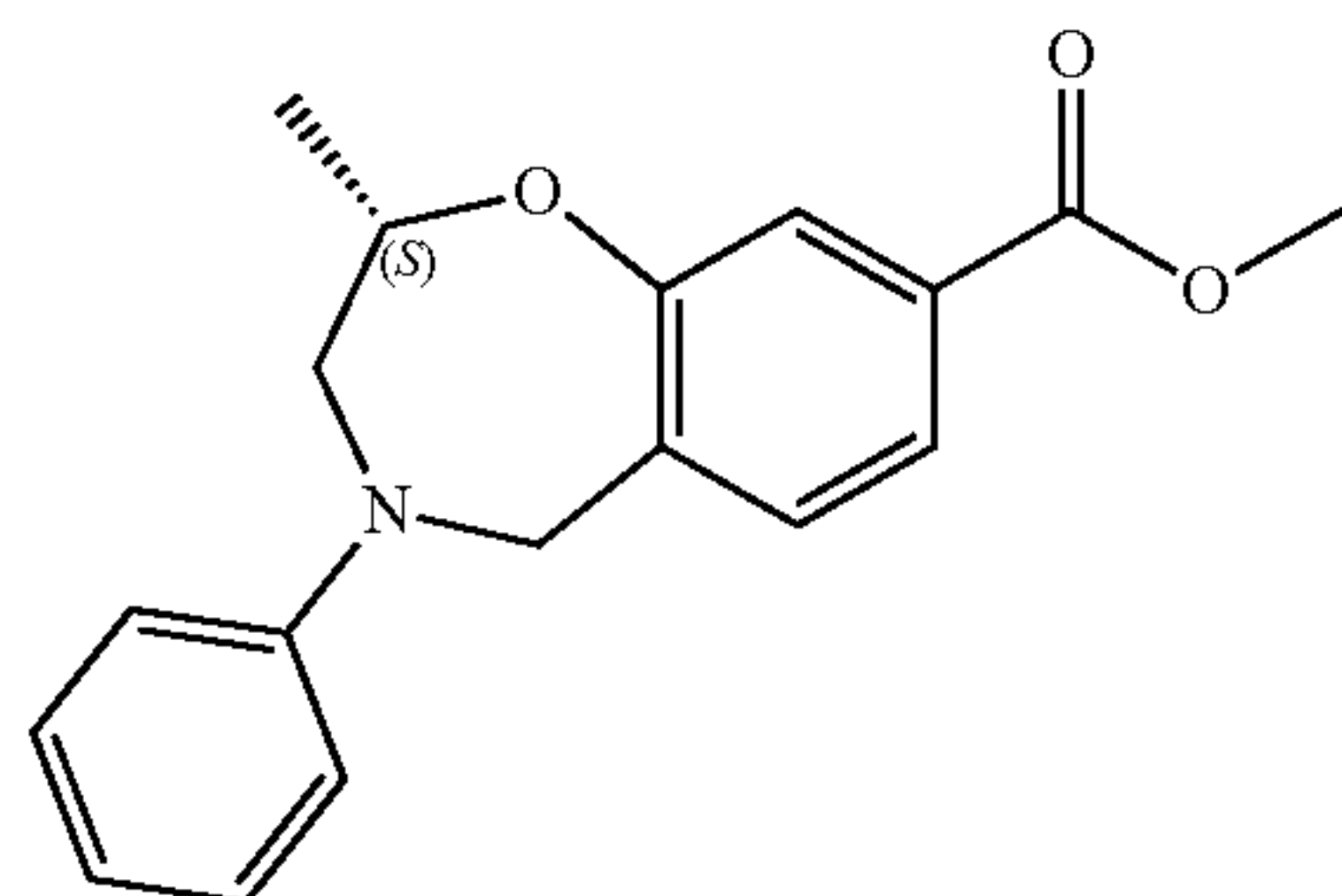
mmol, 1 equiv) in THF/MeOH (4:1, 2 mL). This was followed by the addition of aq. 1N NaOH (0.41 mL, 2 equiv) and NH<sub>2</sub>OH (50% in water, 0.41 mL, 30 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge XP C18 OBD, 5  $\mu$ m, 19 $\times$ 150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 9% B to 60% B in 9 min; Detector: UV 254 nm) to afford the title compound as a pink solid (34 mg, 43% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$ (ppm): 11.17 (br s, 1H), 9.01 (br s, 1H), 7.70-7.66 (m, 2H), 7.42-7.39 (m, 1H), 7.33-7.31 (m, 1H), 7.24 (s, 1H), 7.06-7.02 (m, 2H), 4.57-4.53 (d, J=16 Hz, 1H), 4.25-4.21 (d, J=16 Hz, 1H), 4.04-3.91 (m, 1H), 3.82 (s, 3H), 3.68-3.65 (m, 1H), 3.21-3.18 (m, 1H), 1.26-1.25 (m, J=6.4 Hz, 3H). MS: (ES, m/z): 393 [M+H]<sup>+</sup>.

## Example 20

Preparation of (S)—N-hydroxy-2-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



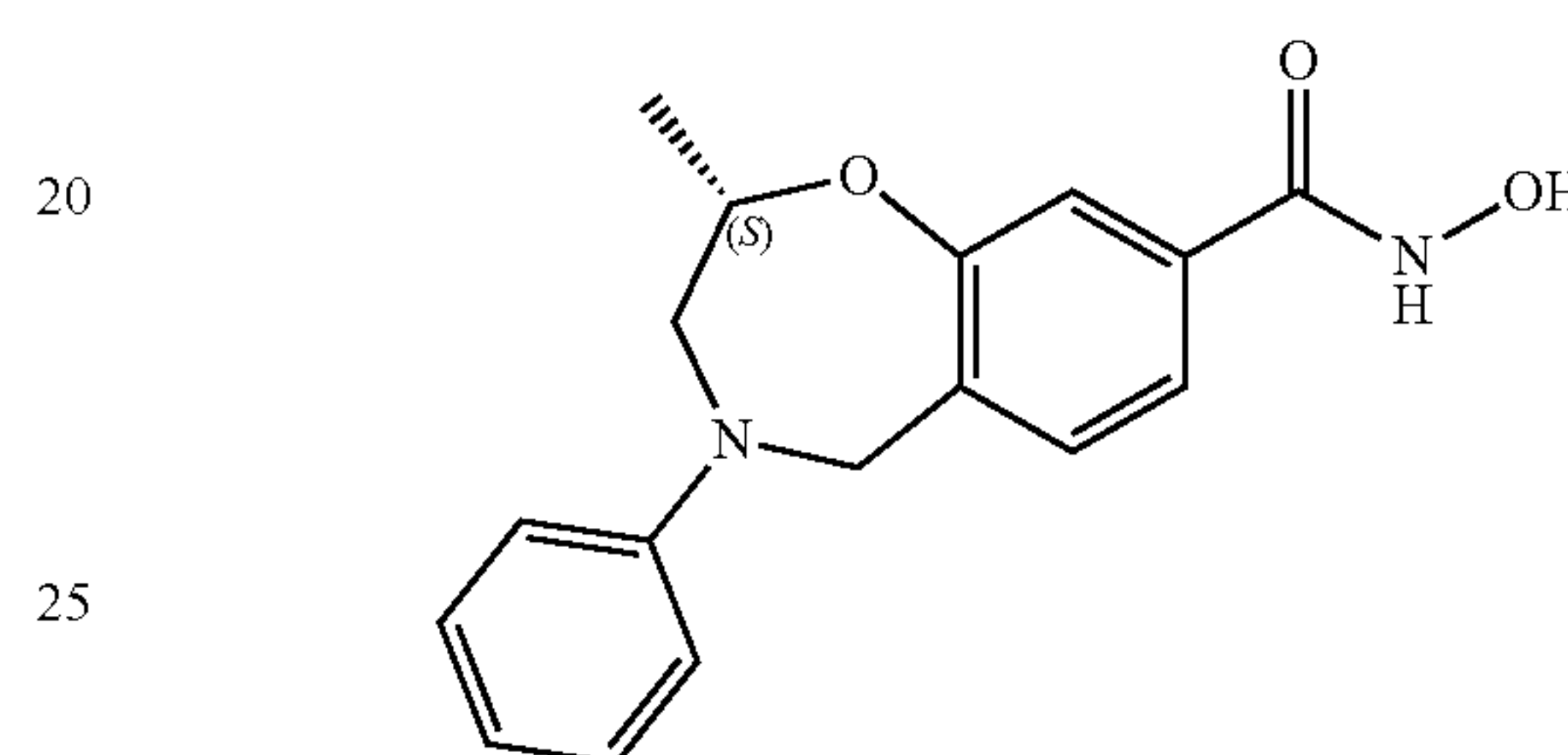
Step-1: Methyl (S)-2-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



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Into a 10-mL vial purged and maintained with Nitrogen, was placed a solution of methyl (S)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv) in 1,4-dioxane (5 mL), iodobenzene (180 mg, 0.88 mmol, 2 equiv), Pd(OAc)<sub>2</sub> (10 mg, 0.04 mmol, 0.1 equiv), Xantphos (50 mg, 0.09 mmol, 0.2 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (450 mg, 1.38 mmol, 3 equiv). The resulting solution was stirred for 10 h at 100° C. and then concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:5) to afford the title compound as a light yellow solid (50 mg, 37% yield). MS: (ES, m/z): 298 [M+H]<sup>+</sup>.

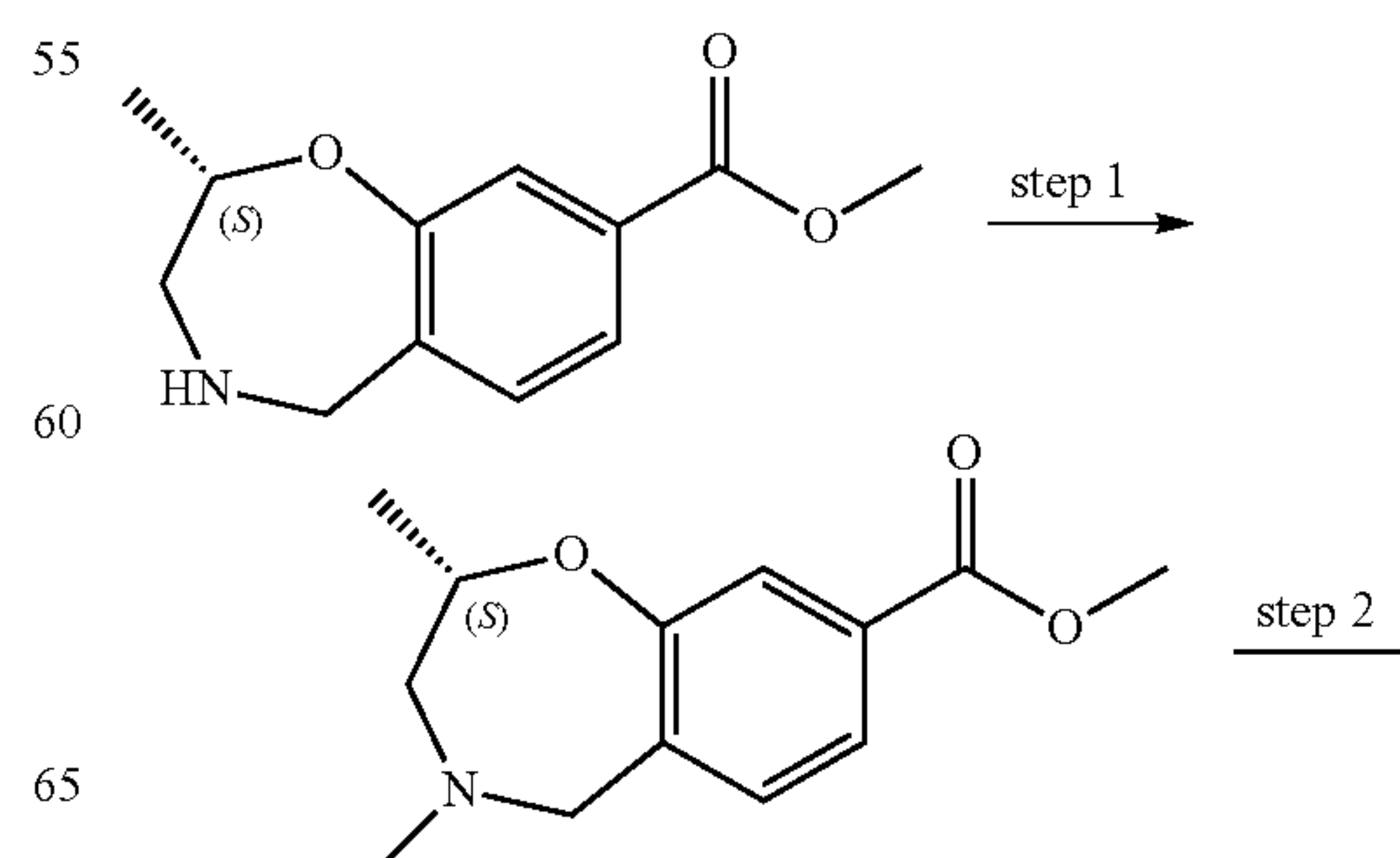
Step-2: (S)—N-Hydroxy-2-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 10-mL vial, was placed a solution of methyl (S)-2-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (50 mg, 0.17 mmol, 1 equiv) in THF/MeOH (4:1, 3 mL). This was followed by the addition of aq. 1N NaOH (0.34 mL, 2 equiv) and NH<sub>2</sub>OH (50% in water, 0.34 mL, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge XP C18 OBD, 5  $\mu$ m, 19 $\times$ 150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 12% B to 48% B in 11 min; Detector: UV 254 nm) to afford the title compound as a brown solid (12 mg, 25% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$ (ppm): 611.09 (br s, 1H), 7.54-7.52 (m, 1H), 7.37-7.35 (m, 1H), 7.34 (s, 1H), 7.29-7.28 (m, 2H), 6.95-6.85 (m, 2H), 6.59-6.55 (m, 1H), 4.83-4.79 (d, J=16 Hz, 1H), 4.62-4.58 (d, J=16 Hz, 1H), 4.08-4.02 (m, 2H), 3.47-3.41 (m, 1H), 1.36-1.24 (m, J=6.4 Hz, 3H). MS: (ES, m/z): 299 [M+H]<sup>+</sup>.

## Example 21

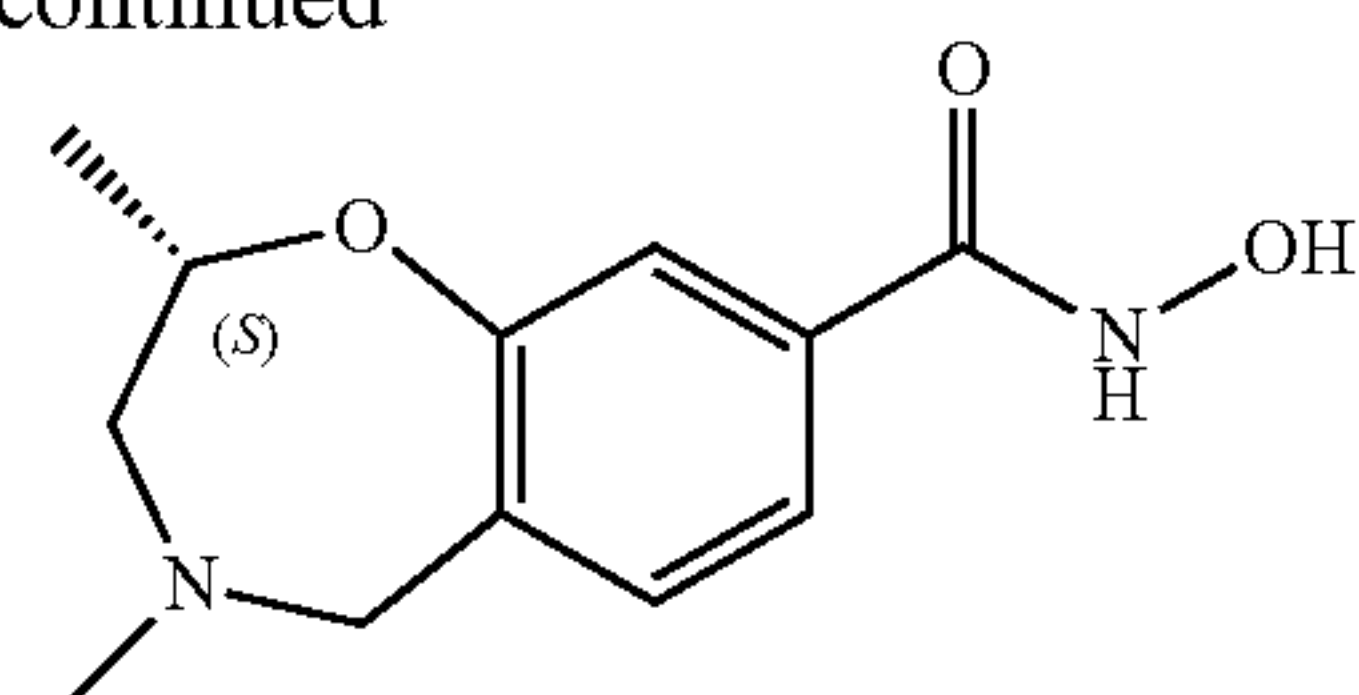
Preparation of (S)—N-hydroxy-2,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



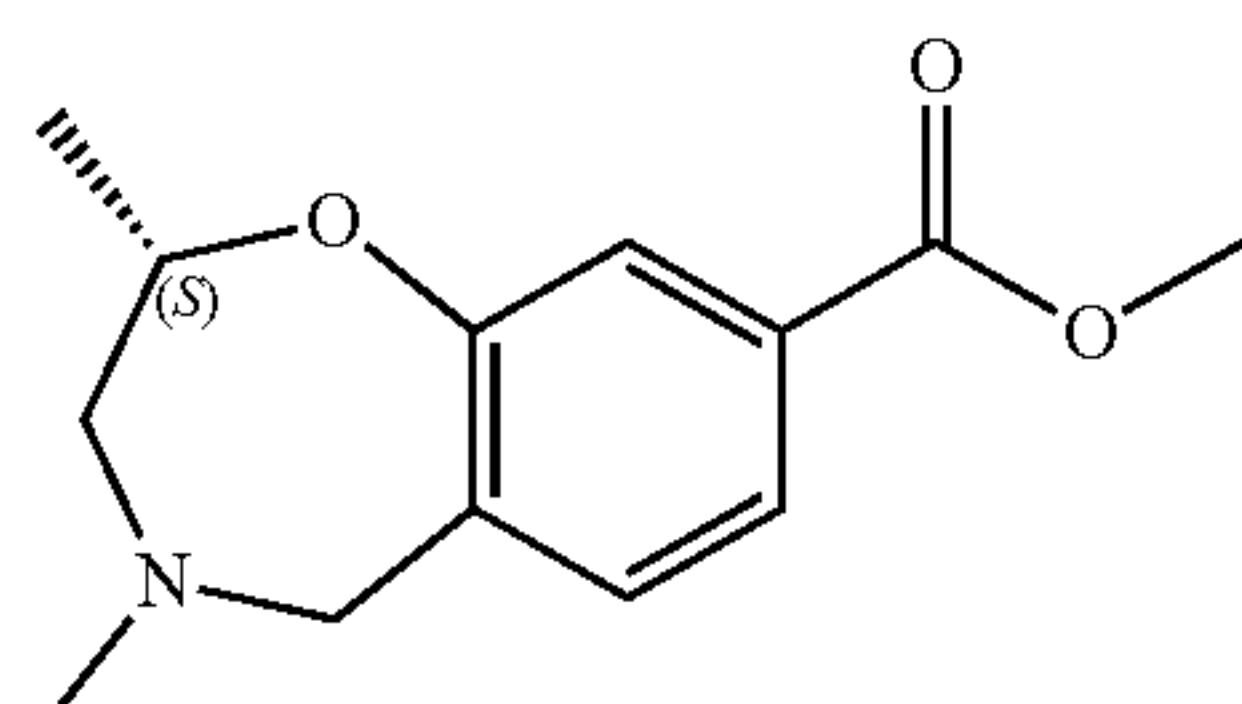


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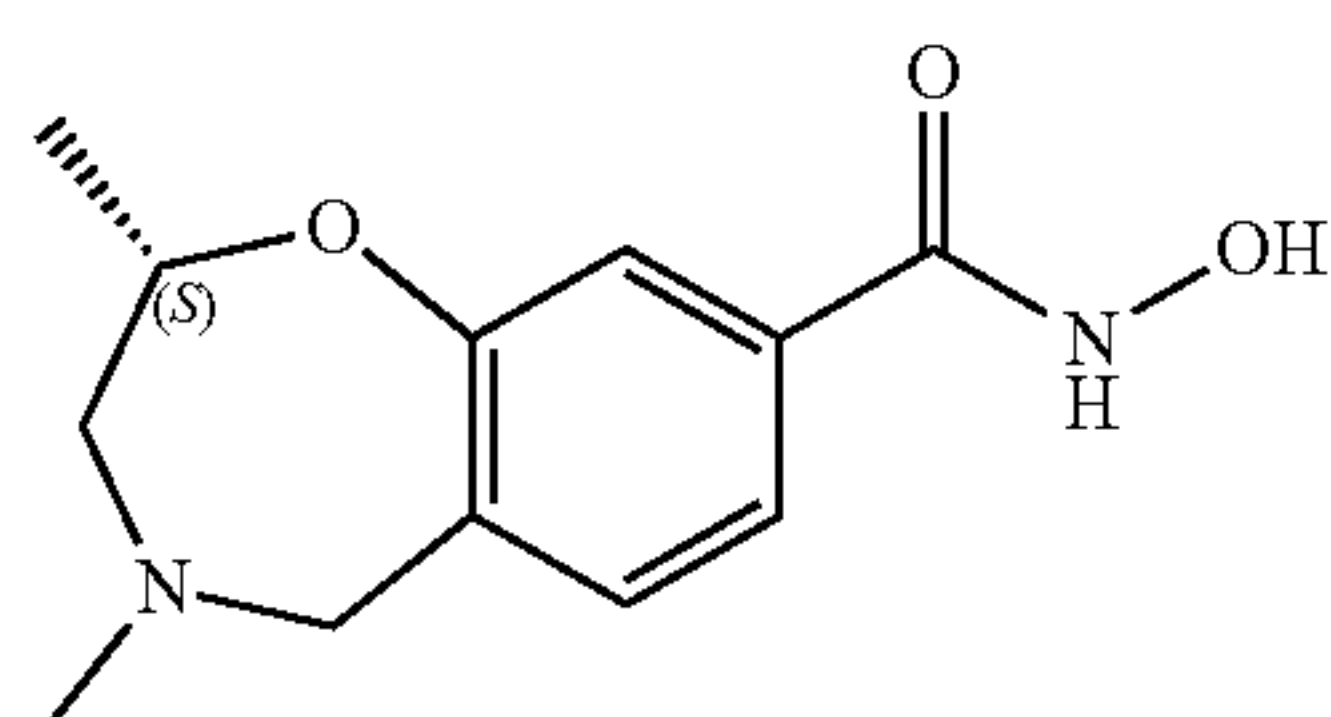


Step-1: Methyl (S)-2,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed methyl (S)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (190 mg, 0.86 mmol, 1 equiv), formaldehyde (78 mg, 2.60 mmol, 3 equiv), acetic acid (2.5 mL) and NaBH(OAc)<sub>3</sub> (907 mg, 4.30 mmol, 5 equiv). The resulting solution was stirred for 16 h at room temperature. The reaction was quenched with water (20 mL). The resulting solution was extracted with EtOAc (2×20 mL), washed with H<sub>2</sub>O (2×15 mL) and concentrated to afford the title compound as yellow oil (100 mg, 49% yield) which was used without further purification. MS: (ES, m/z): 236 [M+H]<sup>+</sup>.

Step-2: (S)—N-hydroxy-2,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

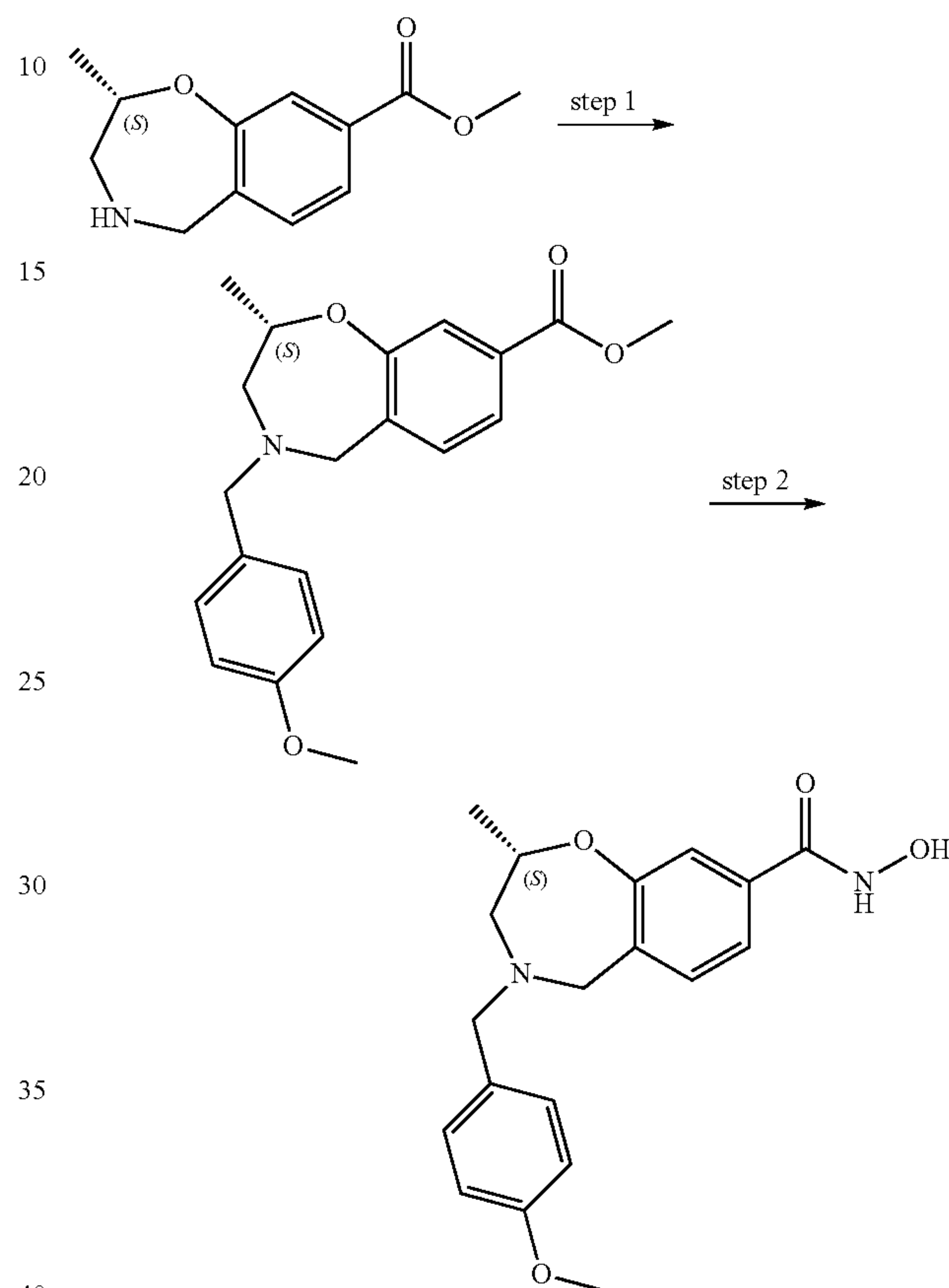


Into a 8-mL vial, was placed methyl (S)-2,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.43 mmol, 1 equiv), THF/MeOH (4:1, 2.5 mL). To this was added aq. 1N NaOH (0.85 mL, 0.85 mmol, 2 equiv) and NH<sub>2</sub>OH (50% in water, 0.86 mL, 12.73 mmol, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge RP C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 40% B in 7 min; Detector: UV 254 nm) to afford the title compound as a light brown solid (37 mg, 37% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.30 (s, 1H), 10.16 (br s, 1H), 9.19 (s, 1H), 7.54-7.52 (m, 1H), 4.46-7.44 (m, 2H), 4.63-4.49 (m, 2H), 3.75-3.48 (m, 2H), 3.11-2.70 (m, 3H), 1.37-1.35 (d, J=6.4 Hz, 3H). MS: (ES, m/z): 237 [M+H]<sup>+</sup>.

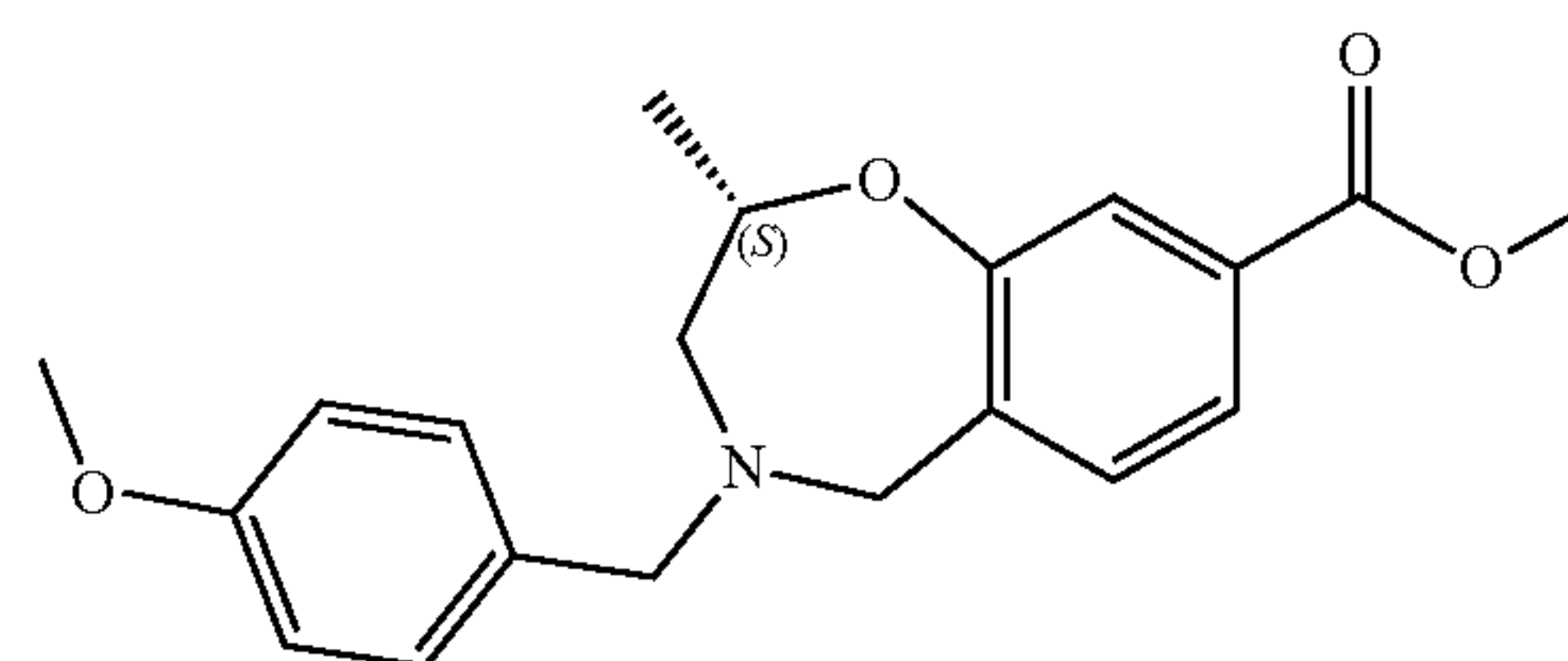
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Example 22

Preparation of (S)—N-hydroxy-4-(4-methoxybenzyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Step-1: Methyl (S)-4-(4-methoxybenzyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



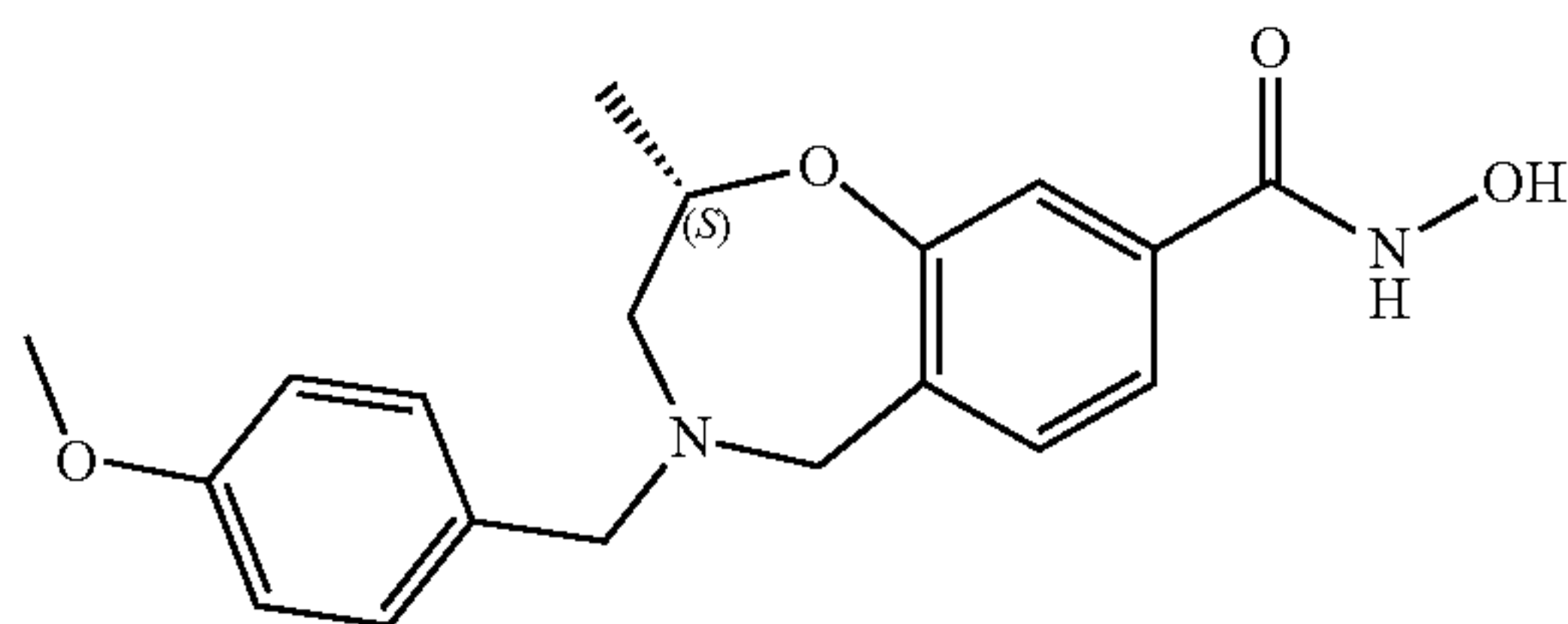
Into a 8-mL vial, was placed methyl (S)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv). This was followed by the addition of sodium hydride (60% in oil, 55 mg, 2.29 mmol, 3 equiv) at 0° C. The mixture was stirred at room temperature for 1 h and then 1-(bromomethyl)-4-methoxybenzene (91 mg, 0.45 mmol, 1 equiv) was added. The mixture was stirred for 19 h at room temperature. The reaction was then quenched with water (20 mL). The resulting solution was extracted with EtOAc (20 mL) and washed with H<sub>2</sub>O (2×15 mL). The



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organic phase was concentrated and the residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a yellow oil (60 mg, 39% yield). MS: (ES,  $m/z$ ): 342  $[M+H]^+$ .

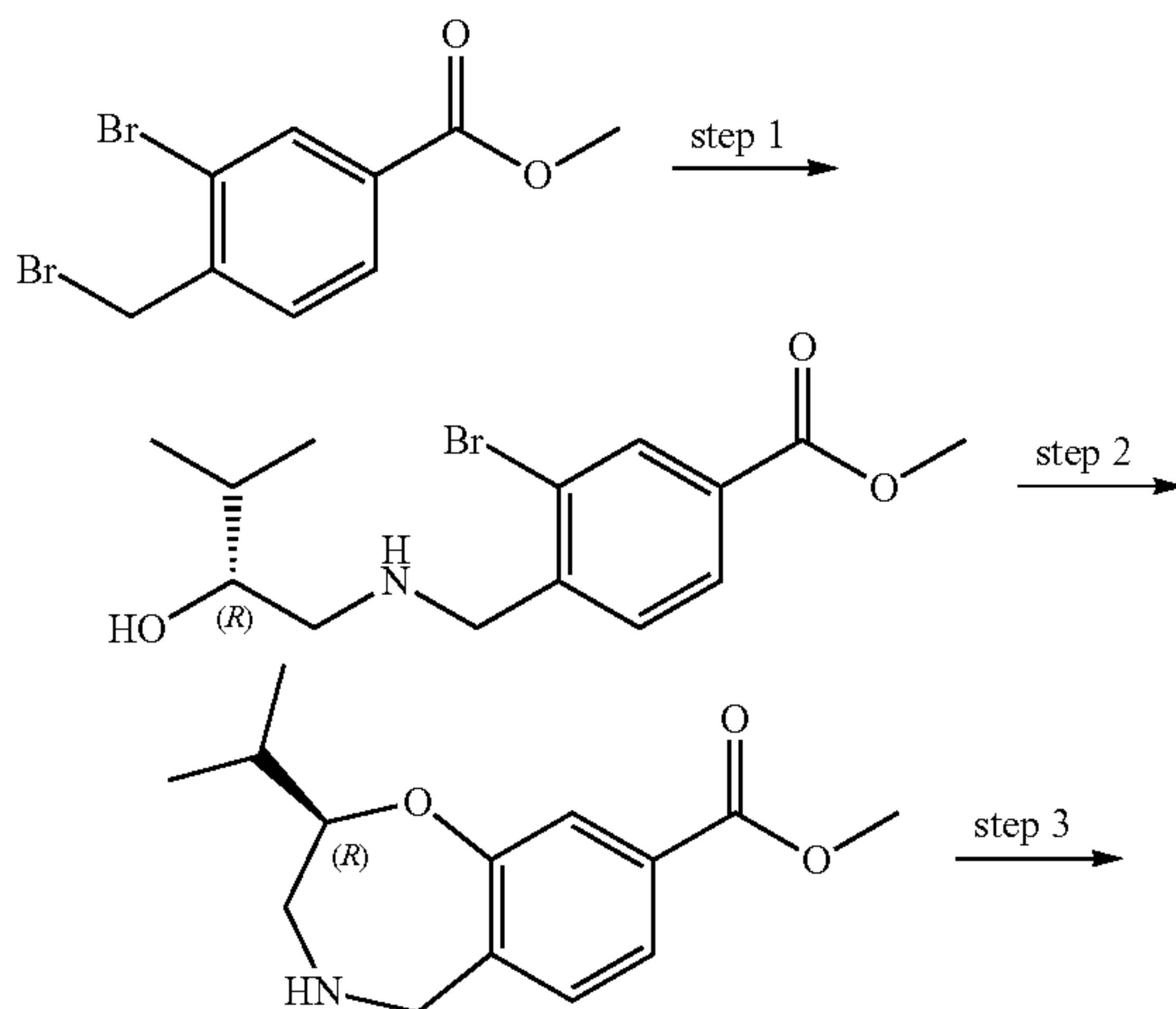
Step-2: (S)—N-hydroxy-4-(4-methoxybenzyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



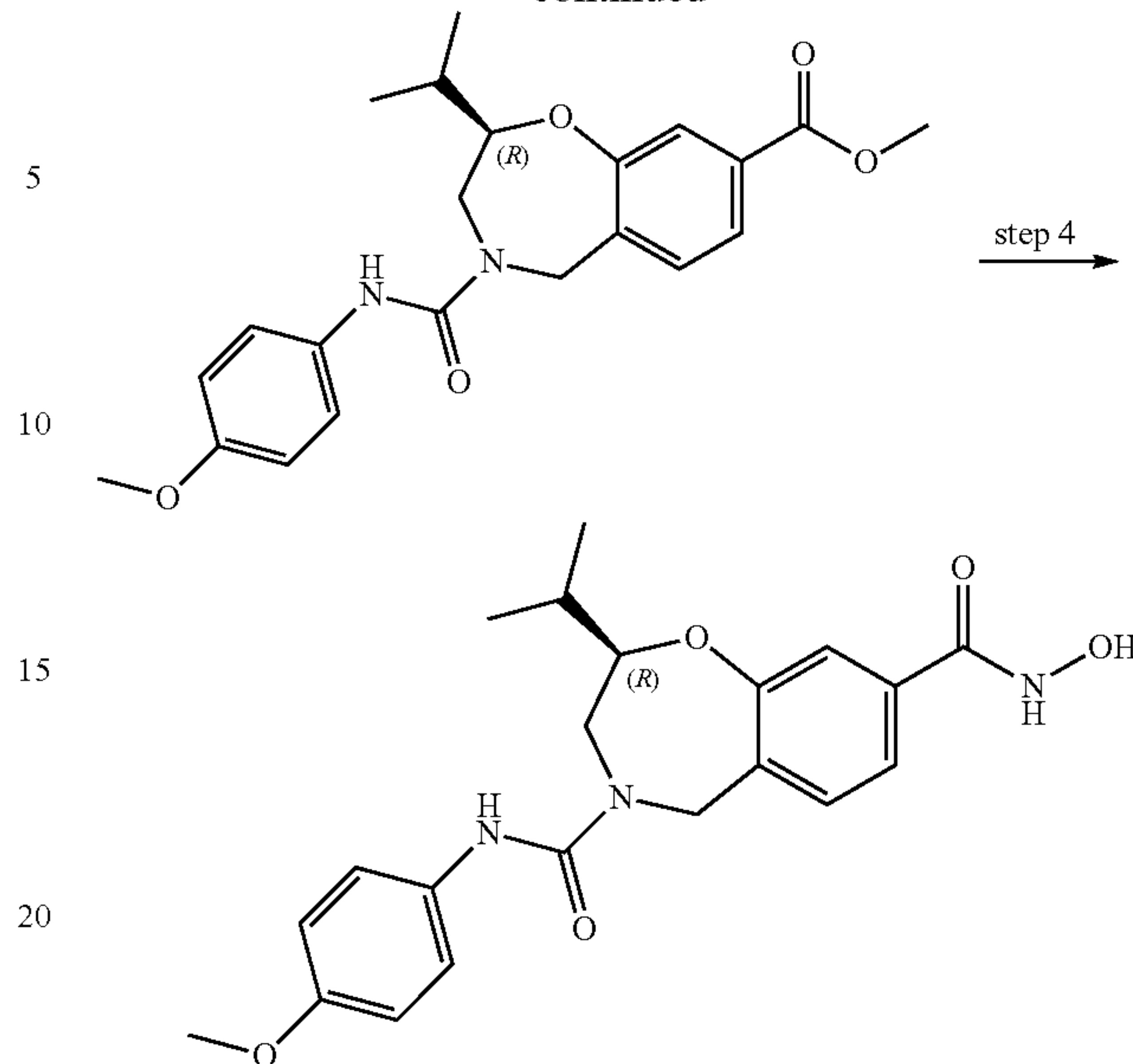
Into a 8-mL vial, was placed methyl (S)-4-(4-methoxybenzyl)-2-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (60 mg, 0.18 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL). To this was added aq. 1N NaOH (0.35 mL, 0.35 mmol, 2 equiv). To the mixture was added  $NH_2OH$  (50% in water, 0.36 mL, 5.27 mmol, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column Sunfire Prep C18 OBD, 5  $\mu m$ , 19 $\times$ 150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 5% B to 30% B in 6 min; Detector: UV 254 nm) to afford the title compound as an off-white solid (21 mg, 26% yield).  $^1H$ -NMR (400 MHz,  $DMSO-d_6$ )  $\delta$ (ppm): 11.17 (s, 1H), 9.13-9.11 (br s, 1H), 7.57-7.28 (m, 5H), 4.67-4.11 (m, 5H), 3.89-3.87 (m, 3H), 3.78-3.56 (m, 2H), 1.34 (s, 3H). MS: (ES,  $m/z$ ): 343  $[M+H]^+$ .

### Example 23

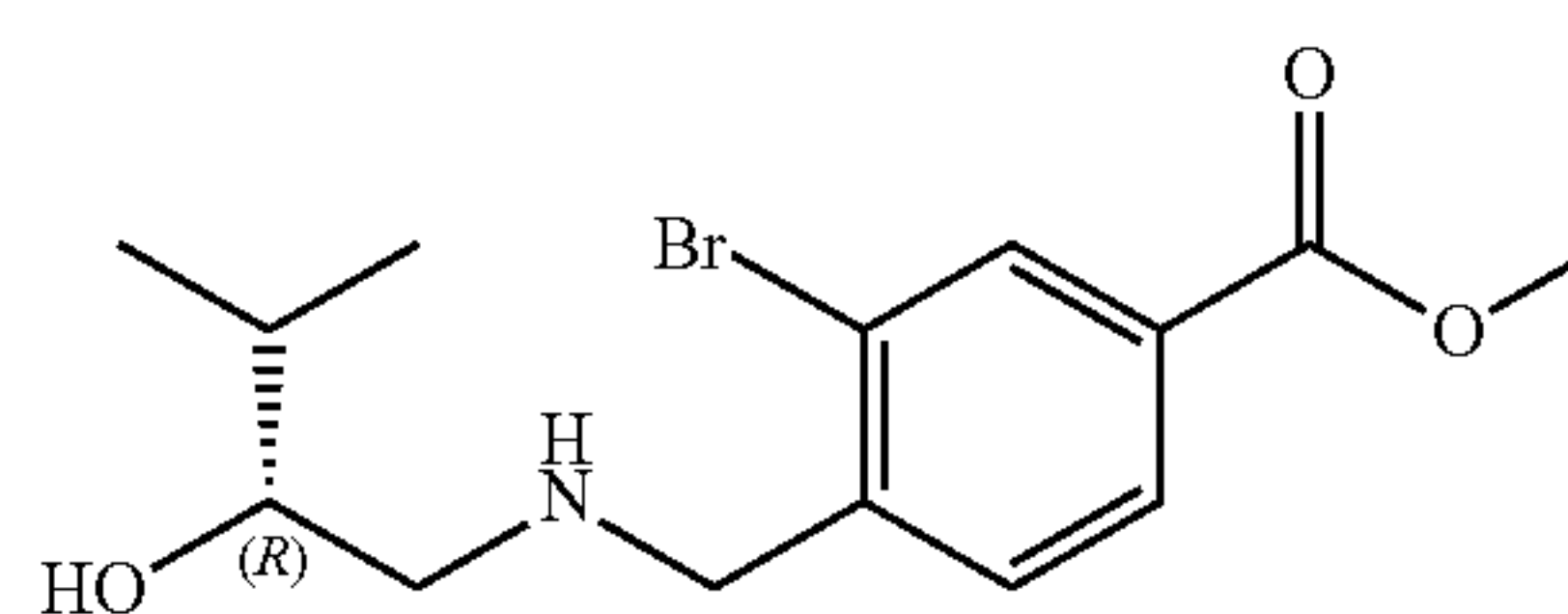
Preparation of (R)—N8-hydroxy-2-isopropyl-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide

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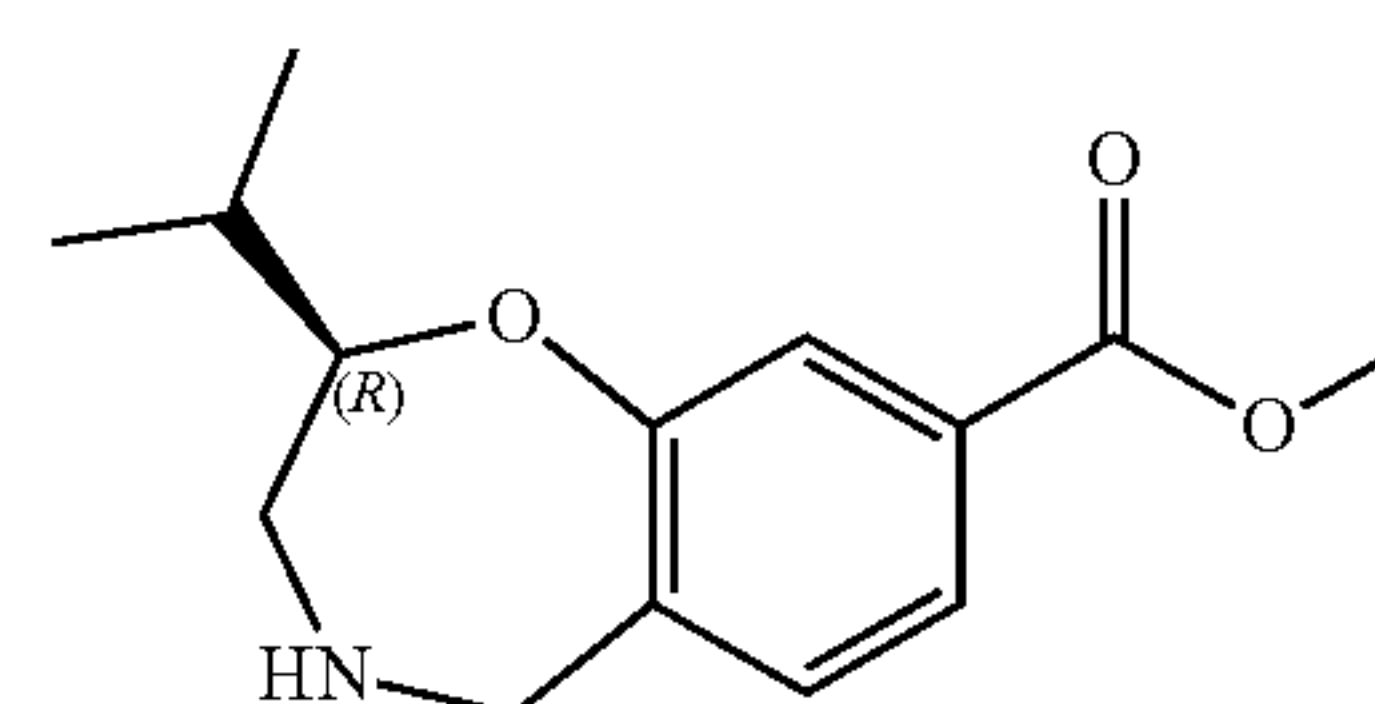


Step-1: Methyl (R)-3-bromo-4-(((2-hydroxy-3-methylbutyl)amino)methyl)benzoate



Into a 500-mL round-bottom flask, was placed (R)-1-amino-3-methylbutan-2-ol (6.41 g, 62.13 mmol, 2 equiv), MeCN (100 mL) and  $K_2CO_3$  (6.44 g, 46.60 mmol, 1.5 equiv). This was followed by the addition of methyl 3-bromo-4-(bromomethyl)benzoate (9.52 g, 30.91 mmol, 1 equiv) in several batches. The resulting solution was stirred for 16 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was dissolved in EtOAc (200 mL) and washed with  $H_2O$  (2 $\times$ 100 mL). The organic layer was dried over anhydrous  $Na_2SO_4$ , filtered, and concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 3:2) to afford the title compound as a yellow solid (6.48 g, 63% yield). MS: (ES,  $m/z$ ): 330  $[M+H]^+$ .

Step-2: Methyl (R)-2-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



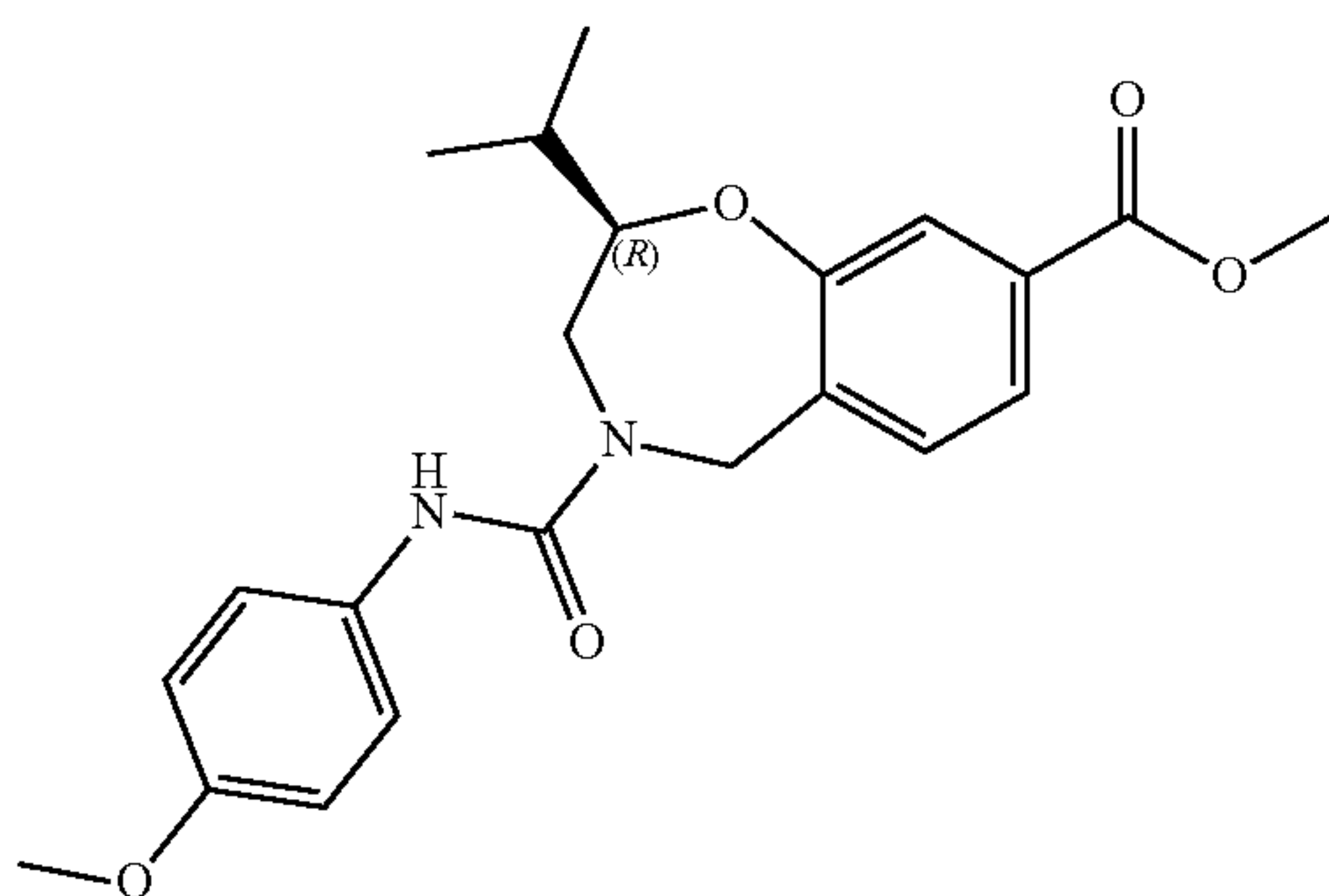
Into a 100-mL pressure tank reactor purged and maintained with an inert atmosphere of nitrogen, was placed



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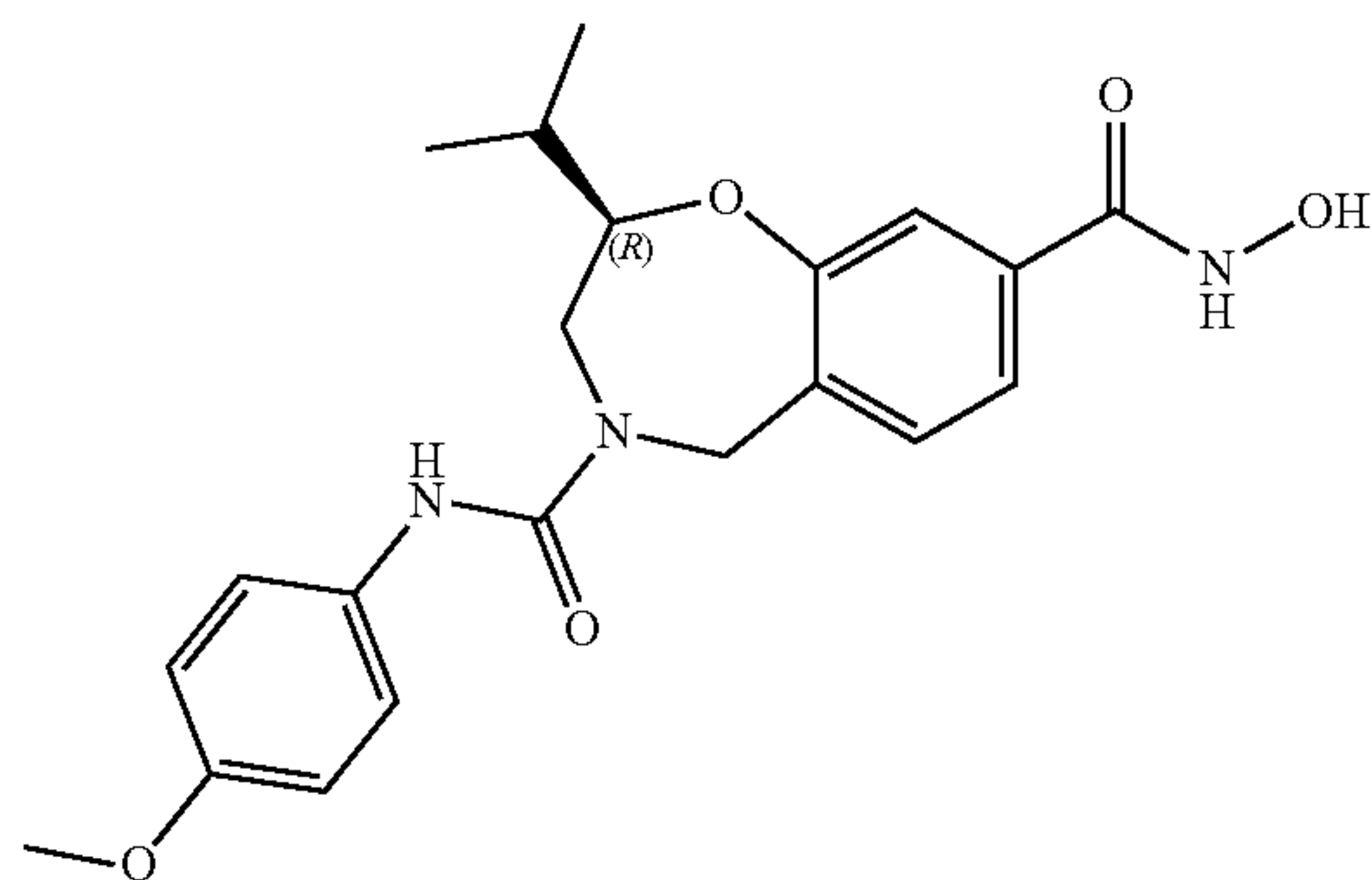
methyl (R)-3-bromo-4-(((2-hydroxy-3-methylbutyl)amino) methyl)benzoate (4.91 g, 14.87 mmol, 1 equiv), isopropanol (50 mL),  $K_2CO_3$  (3.09 g, 22.36 mmol, 1.5 equiv) and CuI (1.42 g, 7.46 mmol, 0.5 equiv). The resulting solution was stirred for 16 h at 110° C. in an oil bath. The resulting mixture was concentrated under vacuum. The residue was dissolved in  $CH_2Cl_2$  (200 mL) and washed with  $H_2O$  (3×100 mL). The organic layer was dried over anhydrous  $MgSO_4$ , filtered, and concentrated. The residue was purified by silica gel chromatography ( $H_2O/MeCN$ , 3:1) to afford the TFA salt of the title compound as a green solid (1.5 g, 40% yield). MS: (ES, m/z): 250  $[M+H]^+$ .

Step-3: Methyl (R)-2-isopropyl-4-((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed methyl (R)-2-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.40 mmol, 1 equiv),  $CH_2Cl_2$  (1.5 mL) and  $Et_3N$  (121 mg, 1.20 mmol, 3 equiv). This was followed by the addition of 1-isocyanato-4-methoxybenzene (90 mg, 0.60 mmol, 1.5 equiv) at 0° C. The resulting solution was stirred for 4 h at room temperature, then concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:2) to afford the title compound as a red oil (110 mg, 69% yield). MS: (ES, m/z): 399  $[M+H]^+$ .

Step-4: (R)—N8-Hydroxy-2-isopropyl-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



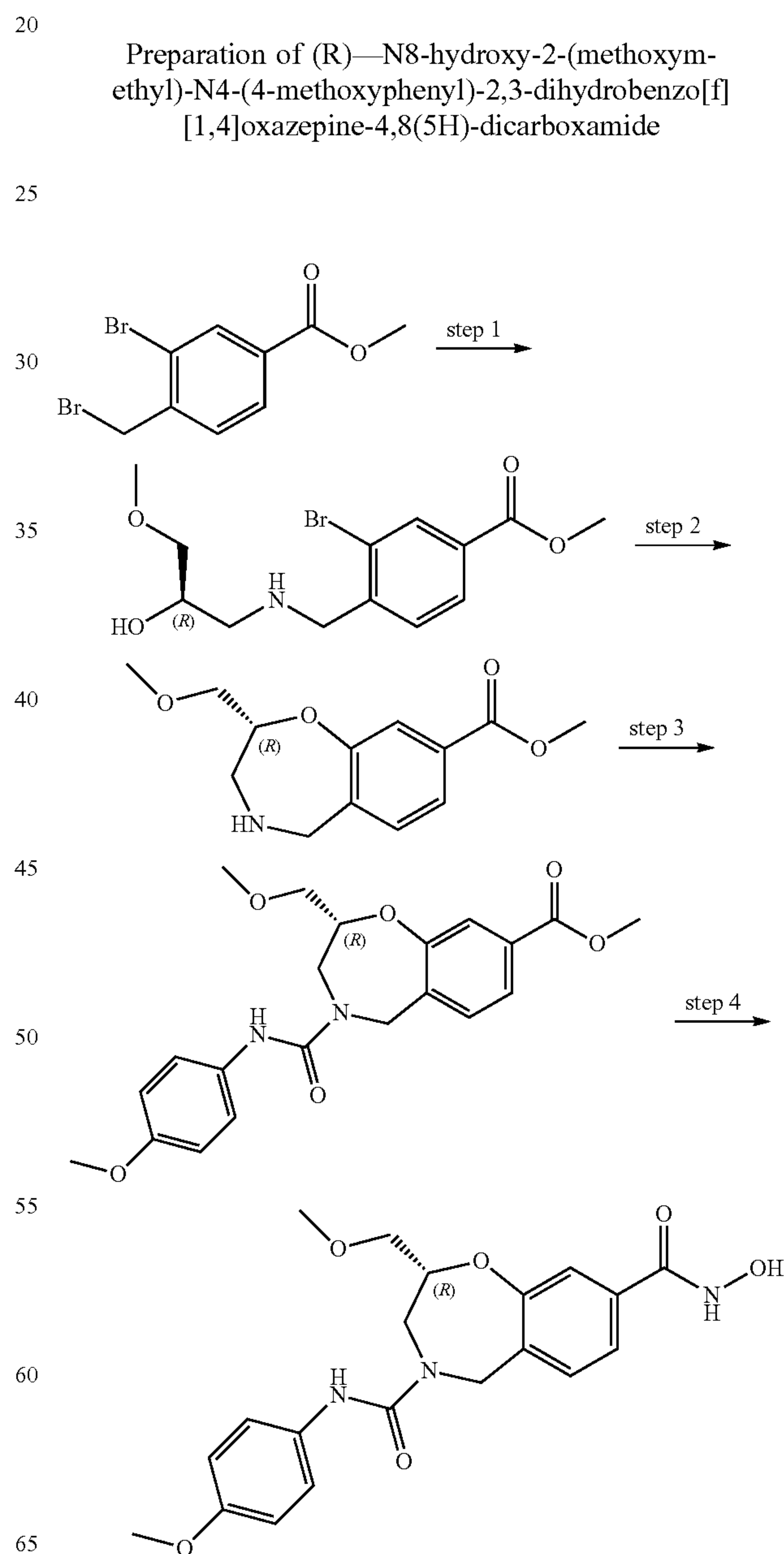
Into a 8-mL vial, was placed methyl (R)-2-isopropyl-4-((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (110 mg, 0.28 mmol, 1 equiv) in THF/MeOH (4:1, 1.5 mL). Then  $NH_2OH$  (50% in water,

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0.56 mL, 8.48 mmol, 30 equiv) and aq. 1N NaOH (0.56 mL, 0.55 mmol, 2 equiv) were added at the same time. The resulting solution was stirred for 16 h at room temperature. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5  $\mu m$ , 19×50 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 23% B to 40% B in 7 min; Detector: UV 254, 220 nm) to afford the title compound as a light pink solid (20.2 mg, 18% yield).  $^1H$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$ (ppm): 11.87 (br s, 1H), 8.40 (s, 1H), 7.45-7.41 (m, 2H), 7.39-7.33 (m, 1H), 7.28-7.26 (m, 2H), 6.80-6.78 (d,  $J=9.2$  Hz, 2H), 4.89-4.85 (d,  $J=16.0$  Hz, 1H), 4.46-4.42 (d,  $J=16.0$  Hz, 1H), 4.11-4.08 (d,  $J=13.6$  Hz, 1H), 3.68 (s, 3H), 3.59-3.55 (m, 1H), 3.48-3.42 (m, 1H), 1.96-1.88 (m, 1H), 1.09-1.06 (m, 6H). MS: (ES, m/z): 400  $[M+H]^+$ .

## Example 24

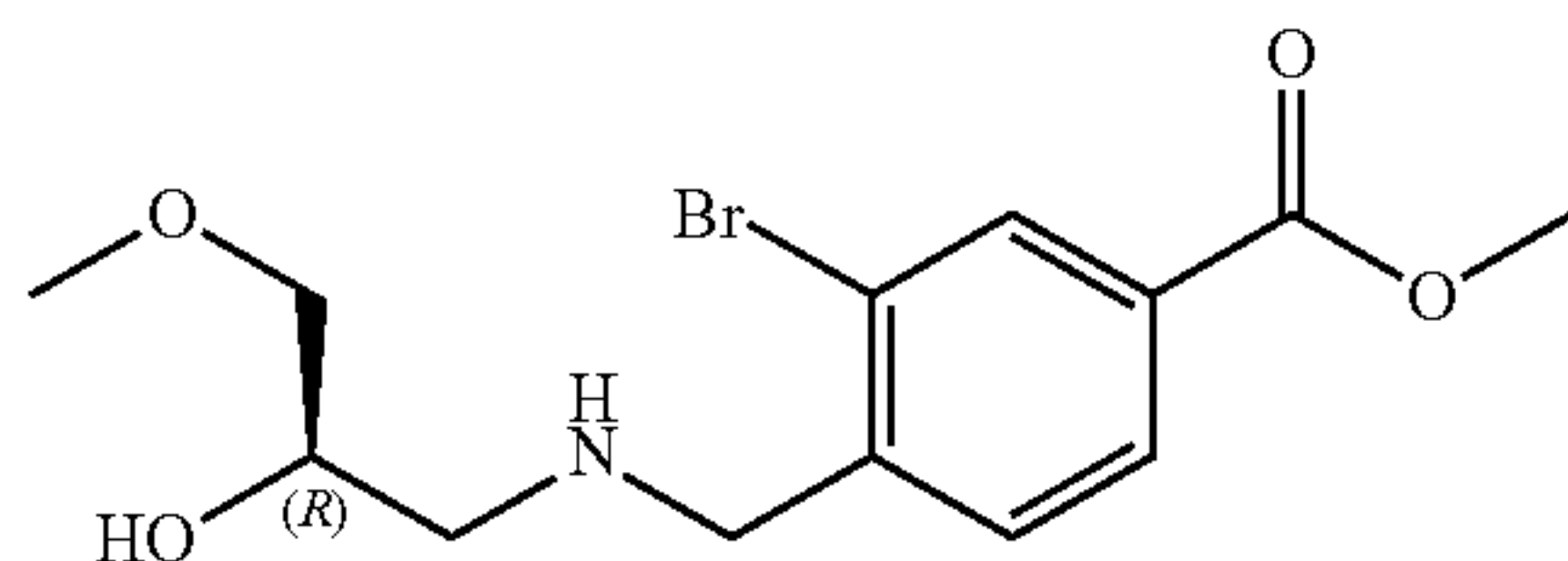
Preparation of (R)—N8-hydroxy-2-(methoxymethyl)-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide





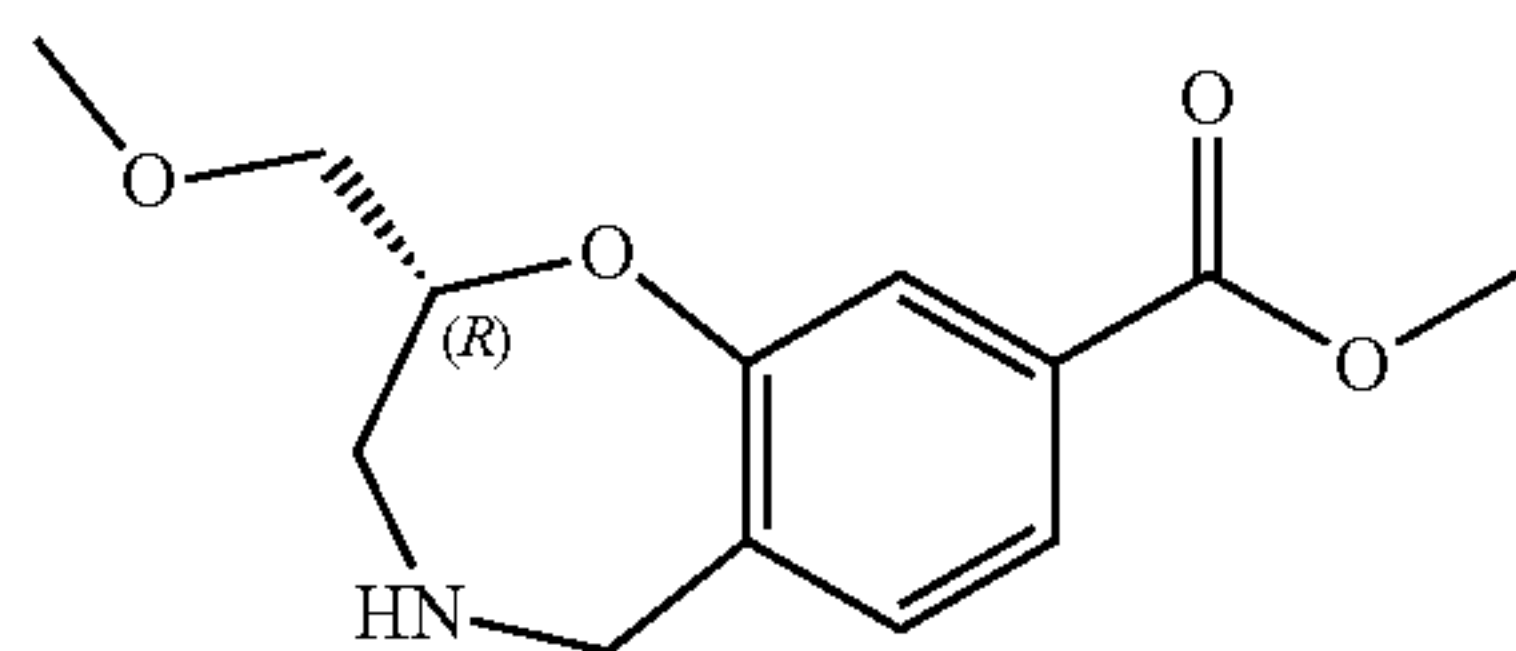
## 85

Step-1: Methyl (R)-3-bromo-4-(((2-hydroxy-3-methoxypropyl)amino)methyl)benzoate



Into a 500-mL round-bottom flask, was placed a solution of (R)-1-amino-3-methoxypropan-2-ol (5.7 g, 54.22 mmol, 1.1 equiv) in MeCN (150 mL) and K<sub>2</sub>CO<sub>3</sub> (10 g, 72.46 mmol, 1.5 equiv). This was followed by the addition of a solution of methyl 3-bromo-4-(bromomethyl)benzoate (15.2 g, 49.36 mmol, 1 equiv) in MeCN (100 mL) dropwise with stirring at room temperature. The resulting mixture was stirred for 16 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (100 mL) and extracted with EtOAc (3×100 mL). The organic layer was washed with H<sub>2</sub>O (2×100 mL) and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:4) to afford the title compound as a yellow solid (6.4 g, 39% yield). MS: (ES, m/z): 332 [M+H]<sup>+</sup>.

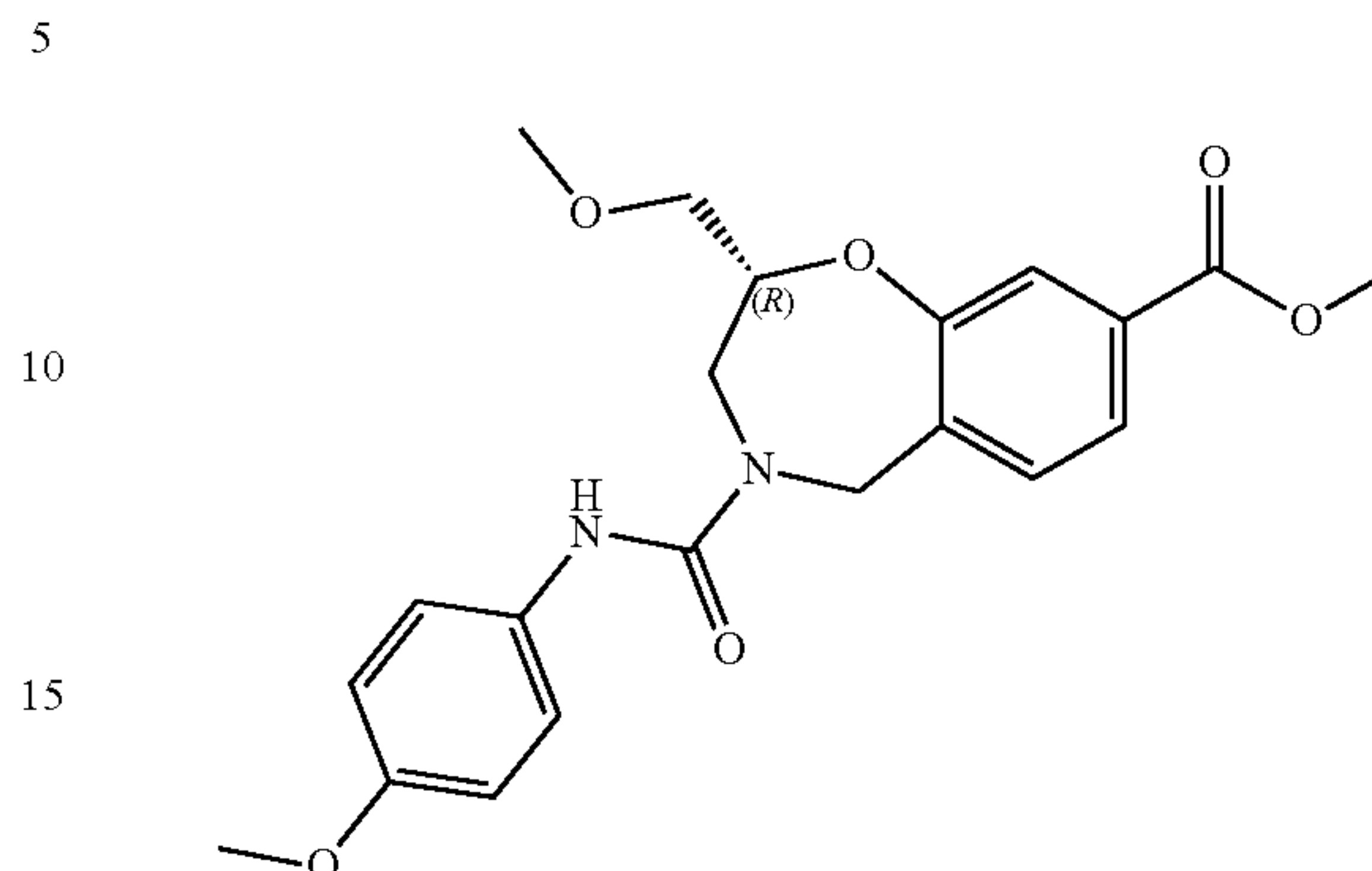
Step-2: Methyl (R)-2-(methoxymethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 150-mL pressure tank reactor purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl (R)-3-bromo-4-(((2-hydroxy-3-methoxypropyl)amino)methyl)benzoate (6.4 g, 19.27 mmol, 1 equiv) in isopropanol (130 mL), K<sub>2</sub>CO<sub>3</sub> (4.01 g, 29.06 mmol, 1.5 equiv) and CuI (1.47 g, 7.74 mmol, 0.4 equiv). The resulting solution was stirred for 16 h at 110° C. in an oil bath. The resulting mixture was concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×100 mL). The organic layer was washed with H<sub>2</sub>O (2×100 mL) and concentrated under vacuum. The residue was purified by C18 chromatography (MeCN/H<sub>2</sub>O+0.05% TFA, 88:12) to afford the TFA salt of the title compound as a yellow solid (3.5 g, 50% yield). MS: (ES, m/z): 252 [M+H]<sup>+</sup>.

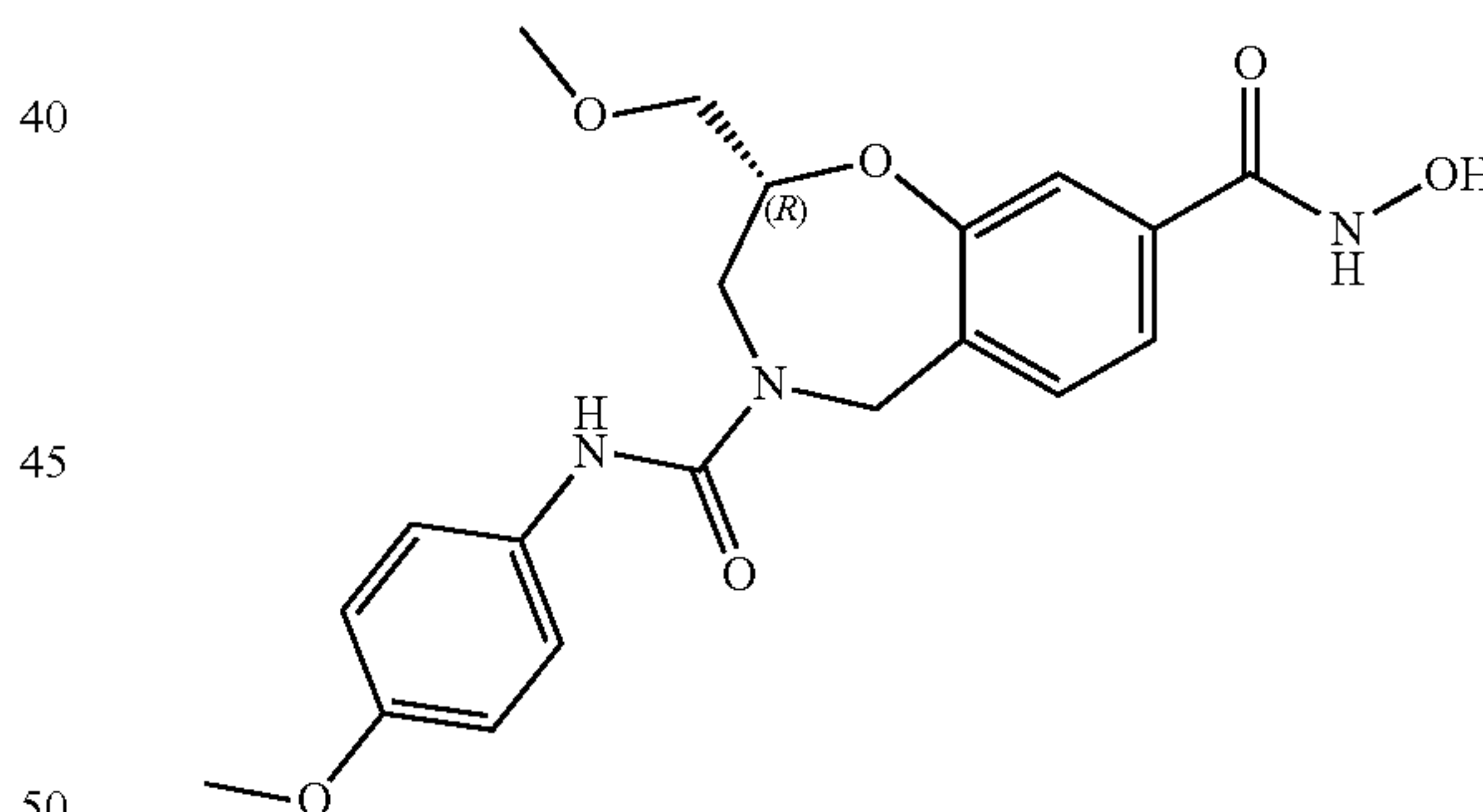
## 86

Step-3: Methyl (R)-2-(methoxymethyl)-4-((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed a solution of methyl (R)-2-(methoxymethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate. TFA (100 mg, 0.27 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), Et<sub>3</sub>N (111 mg, 1.10 mmol, 4 equiv), a solution of 1-isocyanato-4-methoxybenzene (61 mg, 0.41 mmol, 1.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). The resulting mixture was stirred for 6 h at room temperature. The resulting solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and washed with H<sub>2</sub>O (2×15 mL). The combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:2) to afford the title compound as a colorless oil (100 mg, 91% yield). MS: (ES, m/z): 401 [M+H]<sup>+</sup>.

Step-4: (R)—N8-Hydroxy-2-(methoxymethyl)-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



Into a 8-mL vial, was placed a solution of methyl (R)-2-(methoxymethyl)-4-((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.25 mmol, 1 equiv) in THF/MeOH (4:1, 3 mL). Then aq. 1N NaOH (0.50 mL, 2 equiv) and NH<sub>2</sub>OH (50% in H<sub>2</sub>O, 0.50 mL, 30 equiv) were added simultaneously. The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×50 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 23 mL/min; Gradient: 5% B to 39% B in 7 min; Detector: UV 254, 220 nm) to afford the title compound as a light pink solid (62.7 mg, 63% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.15 (br s, 1H), 9.03 (br s, 1H), 8.40 (s, 1H), 7.44-7.739 (m, 2H), 7.36-7.35 (m, 1H), 7.28-7.24 (m, 2H), 6.81-6.77 (m, 2H), 4.87-4.83 (m, 1H), 4.48-4.44 (m, 1H), 4.08-4.03 (m, 2H), 3.68 (s, 3H), 3.61-3.48 (m, 3H), 3.35-3.33 (m, 3H). MS: (ES, m/z): 402 [M+H]<sup>+</sup>.

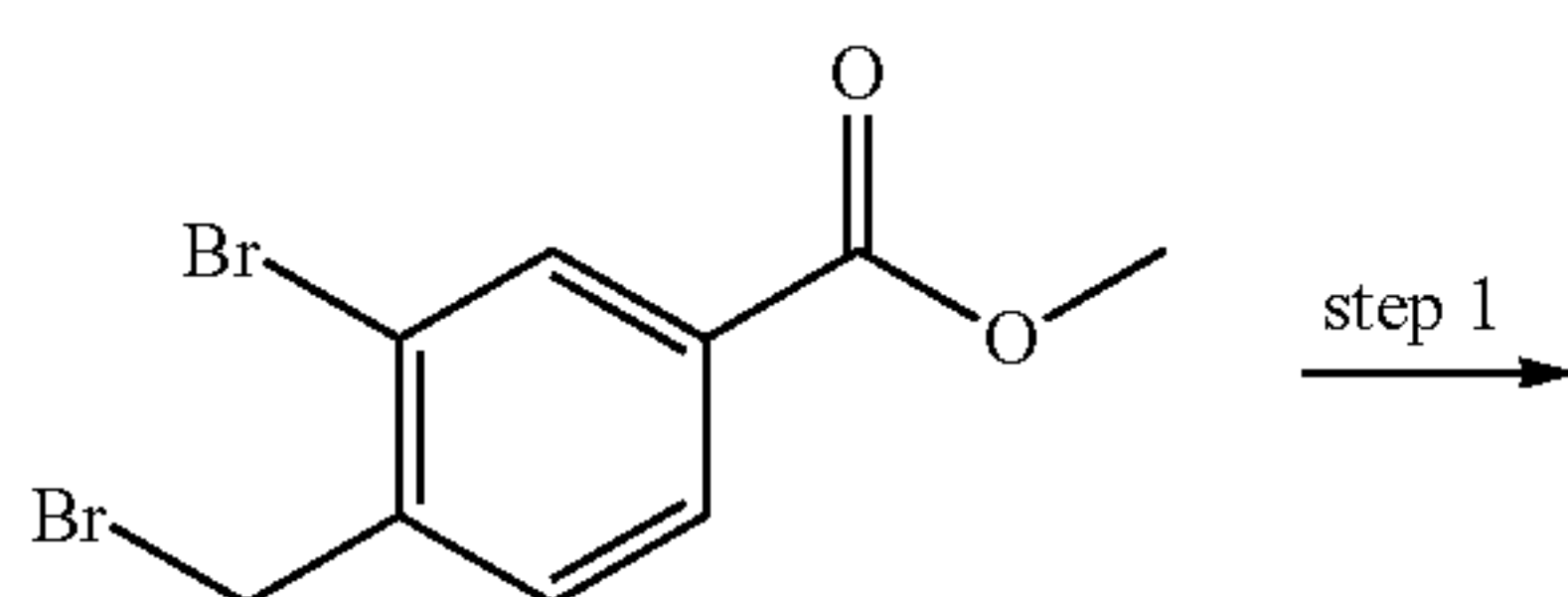


TABLE 6

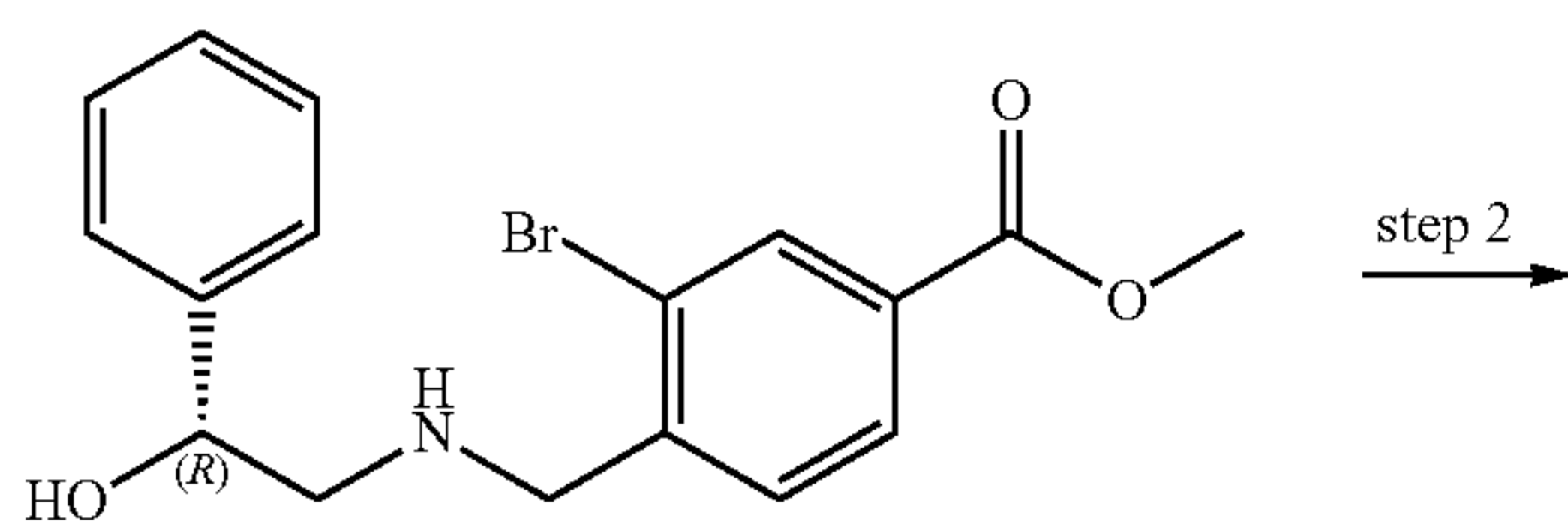
The following compounds were prepared according to the method of Example 24, using (S)-1-amino-3-methoxypropan-2-ol		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 402 [M + H] <sup>+</sup>	11.17 (s, 1H), 9.02 (s, 1H), 8.04 (s, 1H), 7.45-7.41 (m, 2H), 7.40-7.36 (m, 1H), 7.28-7.24 (m, 2H), 6.81-6.77 (m, 2H), 4.87-4.83 (d, J = 15.6 Hz, 1H), 4.48-4.44 (d, J = 15.6 Hz, 1H), 4.08-4.03 (m, 2H), 3.68 (s, 3H), 3.61-3.48 (m, 3H), 3.35-3.33 (d, J = 9.2 Hz, 2H)

## Example 25

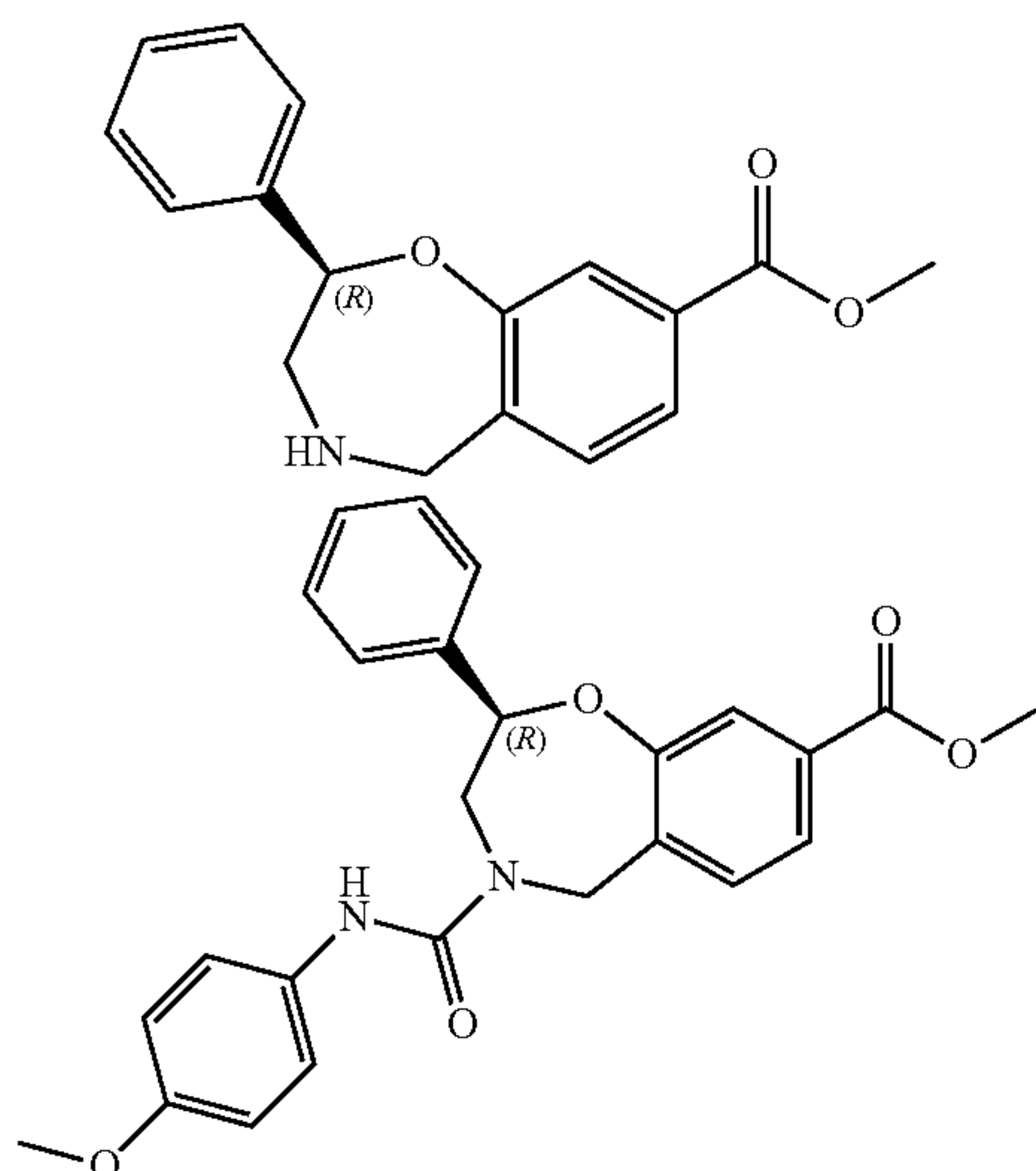
Preparation of (R)—N8-hydroxy-N4-(4-methoxyphenyl)-2-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



step 1



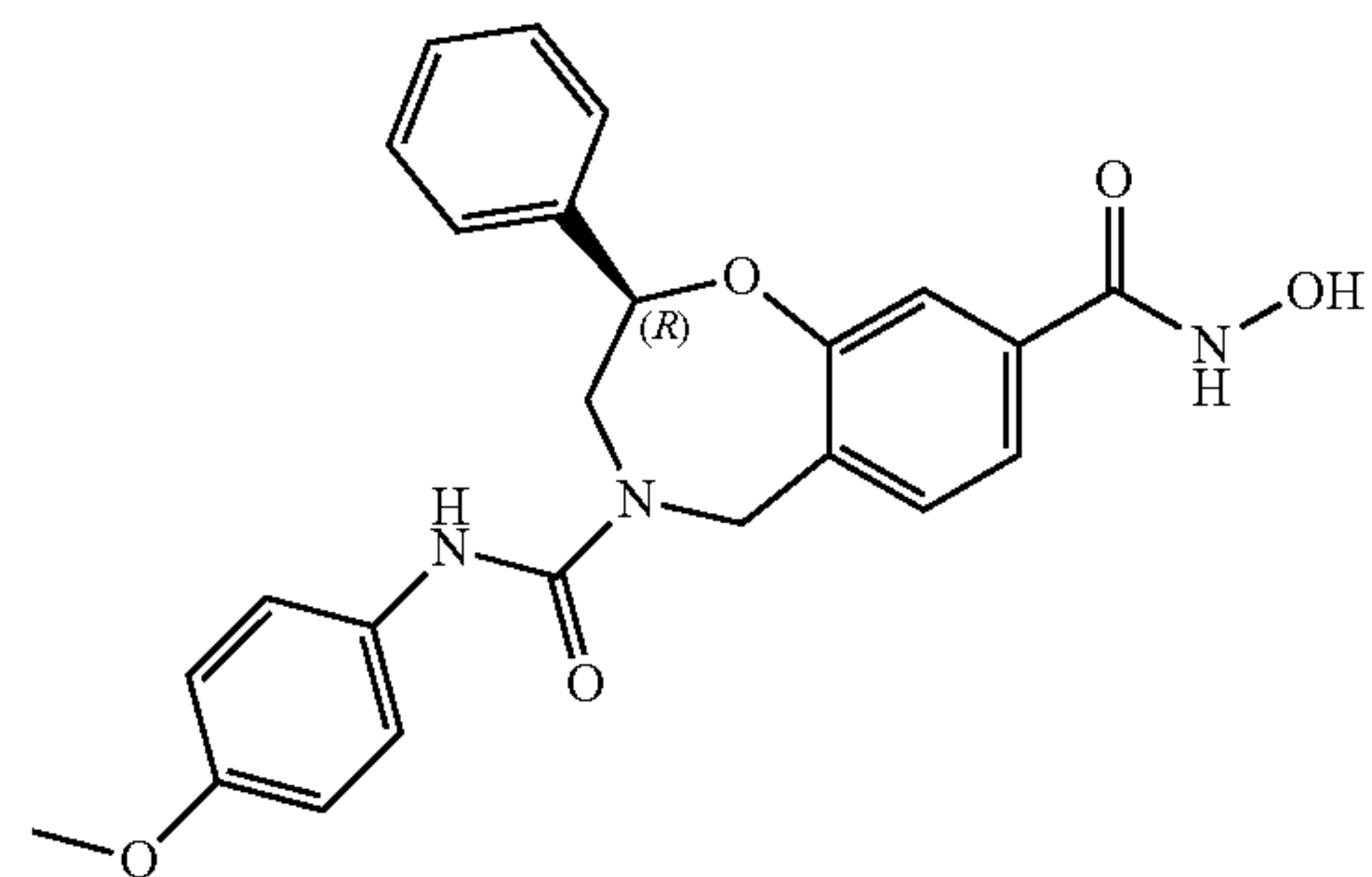
step 2



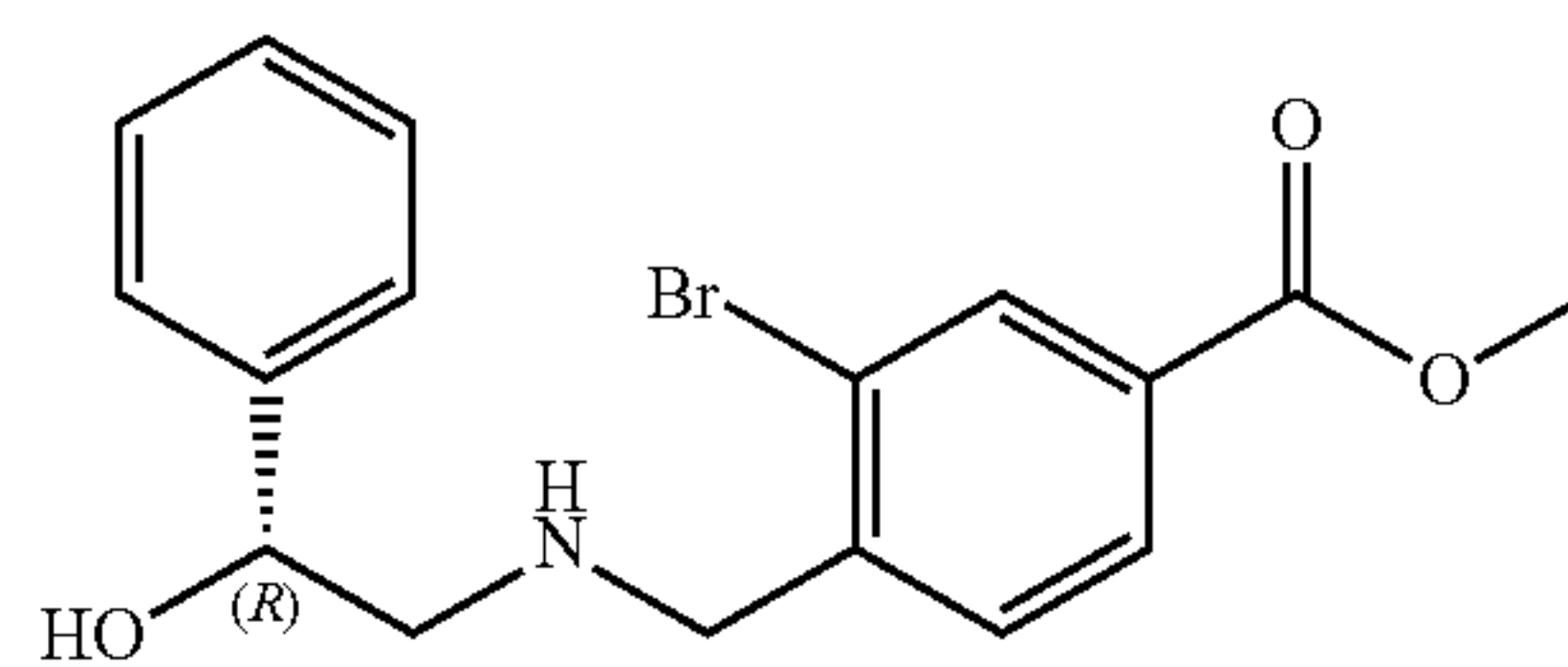
step 3

step 4

-continued



Step-1: Methyl (R)-3-bromo-4-(((2-hydroxy-2-phenylethyl)amino)methyl)benzoate



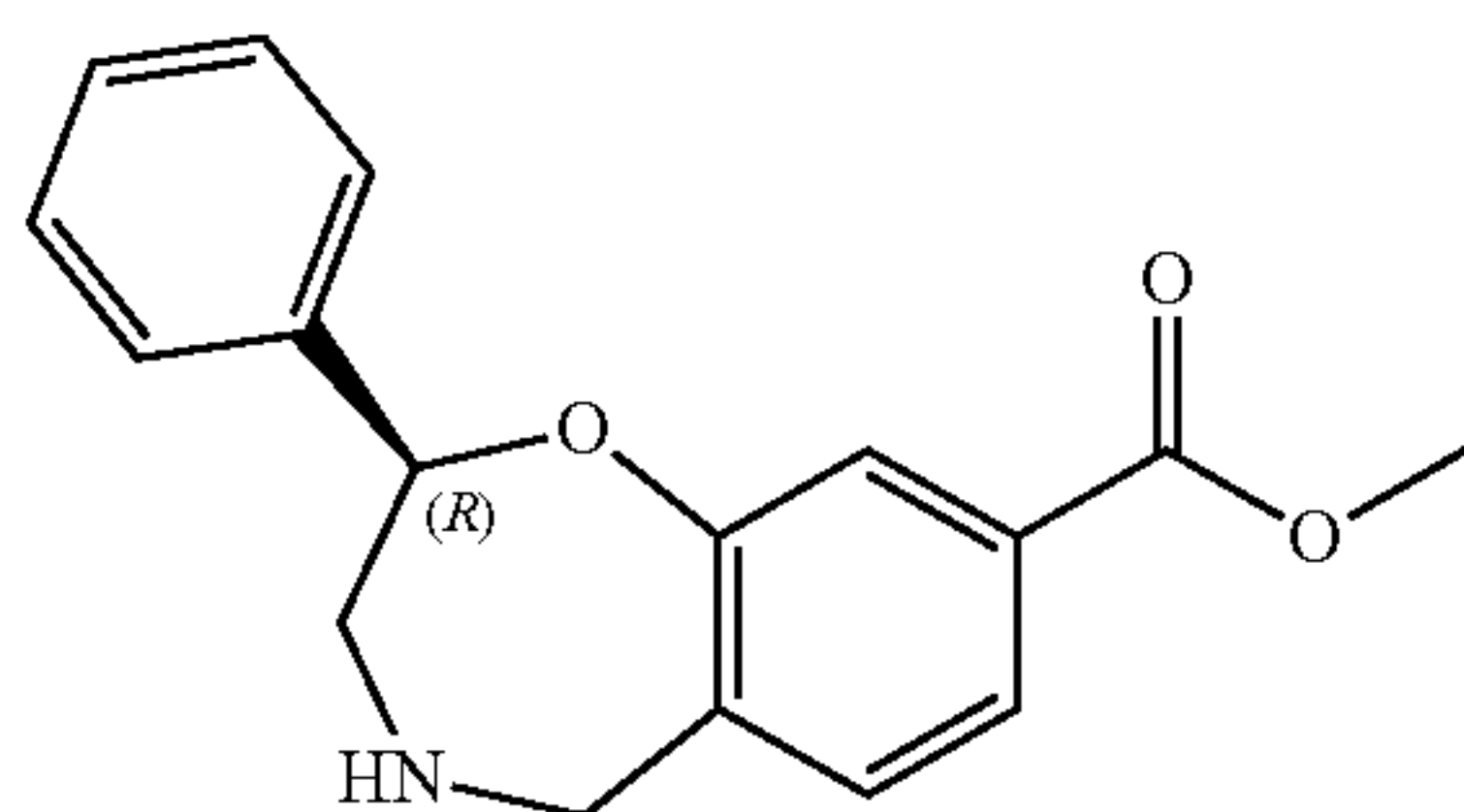
Into a 500-mL round-bottom flask, was placed a solution of (R)-2-amino-1-phenylethan-1-ol (10 g, 72.90 mmol, 1.5 equiv) in MeCN (100 mL), then K<sub>2</sub>CO<sub>3</sub> (8.7 g, 62.49 mmol, 1.3 equiv) was added. This was followed by the slow addition of a solution of methyl 3-bromo-4-(bromomethyl)benzoate (15 g, 48.71 mmol, 1 equiv) in MeCN (120 mL). The resulting mixture was stirred overnight at room temperature and then concentrated under vacuum. The residue was dissolved in EtOAc (350 mL) and washed with H<sub>2</sub>O (3×100 mL). The organic layer was concentrated under vacuum and purified by silica gel chromatography (EtOAc/



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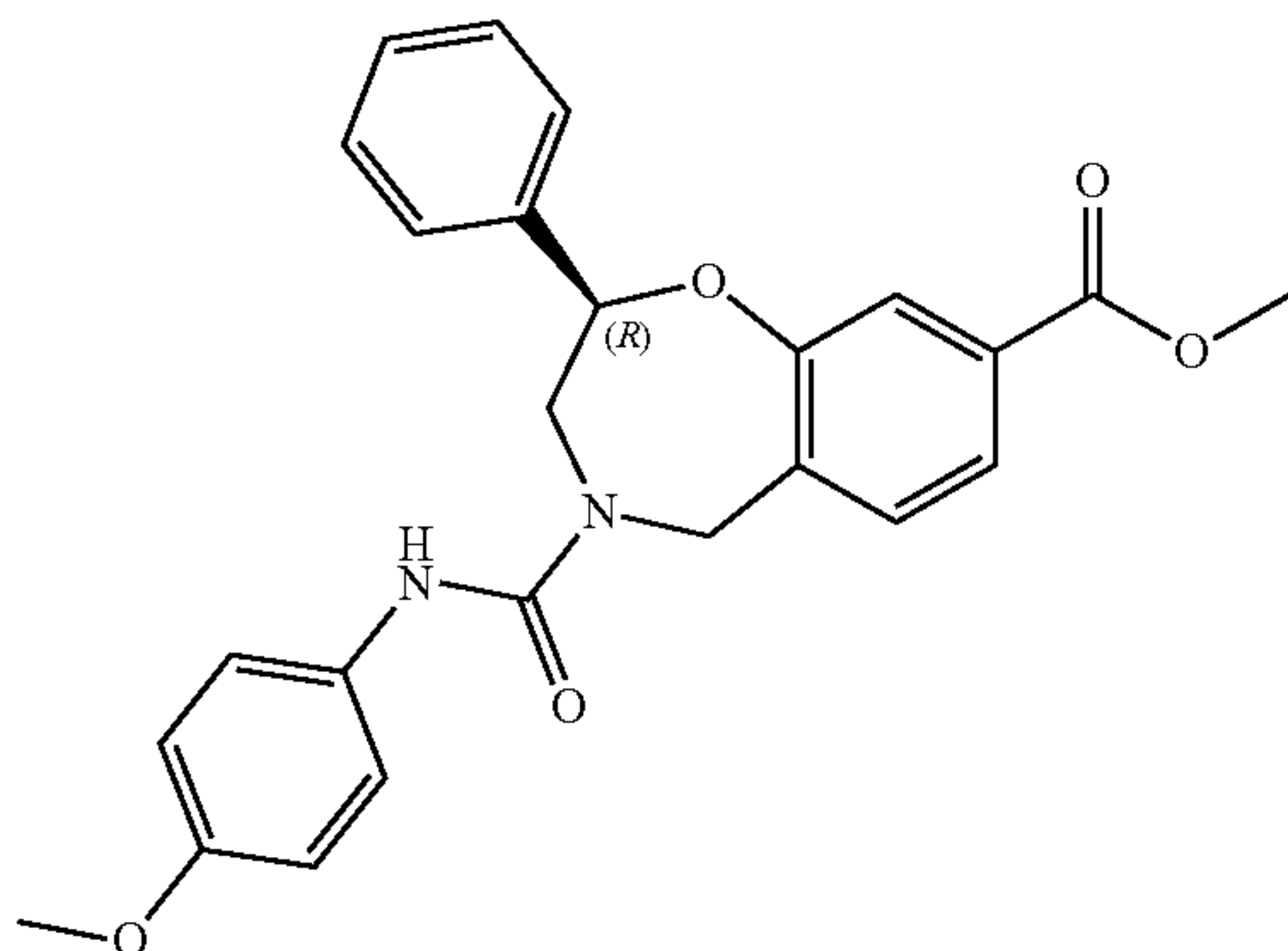
pet. ether, 1:3) to afford the title compound as a yellow solid (9.7 g, 57% yield). MS: (ES, m/z): 364 [M+H]<sup>+</sup>.

Step-2: Methyl (R)-2-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 100-mL sealed tube, was placed a solution of methyl (R)-3-bromo-4-(((2-hydroxy-2-phenylethyl)amino)methyl)benzoate (4.0 g, 10.98 mmol, 1 equiv) in isopropanol (80 mL), then K<sub>2</sub>CO<sub>3</sub> (3.1 g, 22.43 mmol, 2 equiv) was added. This was followed by the addition of CuI (630 mg, 3.31 mmol, 0.3 equiv). The resulting mixture was stirred overnight at 110° C. in an oil bath. The solids were filtered out and the filtrate was concentrated under vacuum. The residue was dissolved in EtOAc (300 mL) and washed with H<sub>2</sub>O (3×150 mL). The organic layer was concentrated under vacuum. The residue was dissolved in DMF and purified by Flash-Prep-HPLC (Mobile Phase A: Water/0.05% TFA, Mobile Phase B: MeCN; Gradient: 5% B to 20% B in 15 min; Detector: 220, 254 nm) to afford the TFA salt of the title compound as a white solid (1.9 g, 61% yield). MS: (ES, m/z): 284 [M+H]<sup>+</sup>.

Step-3: Methyl (R)-4-((4-methoxyphenyl)carbamoyl)-2-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

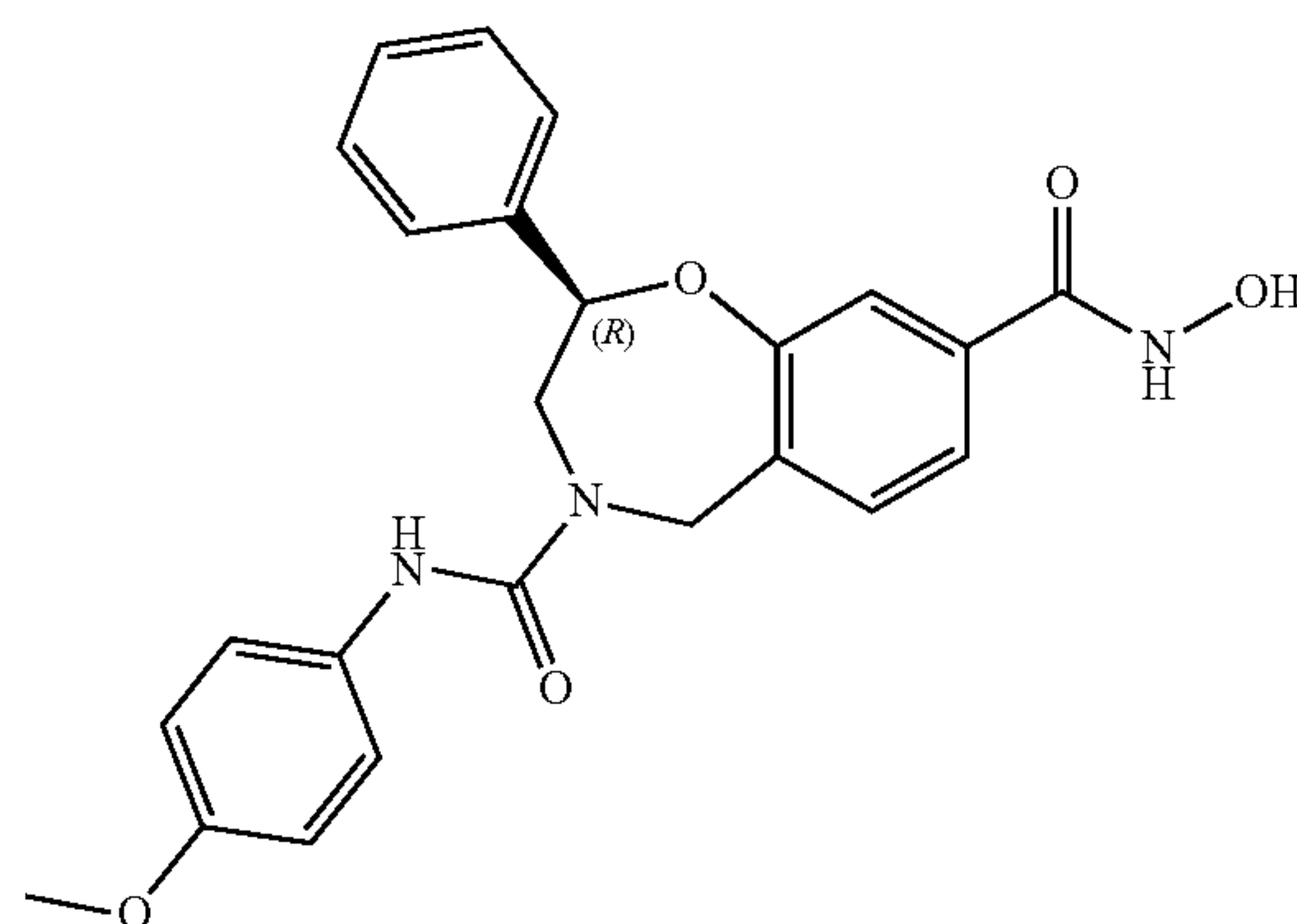


Into a 8-mL vial, was placed a solution of methyl (R)-2-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-car

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boxylate.TFA (100 mg, 0.35 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL). This was followed by the addition of Et<sub>3</sub>N (76.13 mg, 0.75 mmol, 3 equiv) at 0° C. To this was added 1-isocyanato-4-methoxybenzene (56.2 mg, 0.38 mmol, 1.5 equiv). The resulting mixture was stirred for 6 h at room temperature and diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The resulting mixture was washed with H<sub>2</sub>O (3×15 mL) and the combined organic layers were concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a yellow oil (105 mg, 69% yield). MS: (ES, m/z): 433 [M+H]<sup>+</sup>.

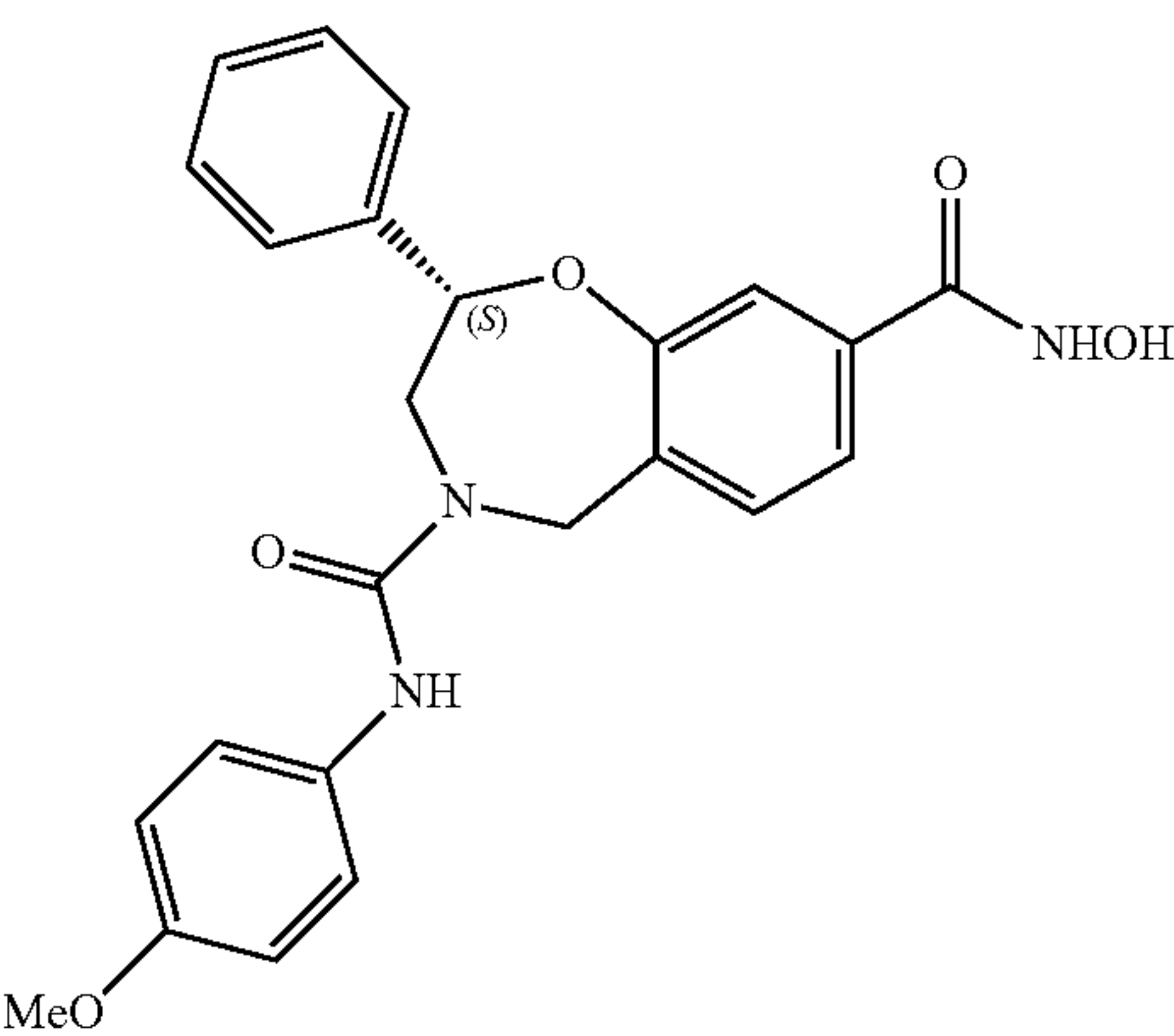
Step-4: (R)—N8-Hydroxy-N4-(4-methoxyphenyl)-2-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8 (5H)-dicarboxamide



Into a 8-mL vial, was placed a solution of methyl (R)-4-((4-methoxyphenyl)carbamoyl)-2-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (105 mg, 0.24 mmol, 1 equiv) in THF/MeOH (4:1, 2.5 mL). Then aq. 1N NaOH (0.48 mL, 2 equiv) and NH<sub>2</sub>OH (50% in H<sub>2</sub>O, 0.48 mL, 30 equiv) were added simultaneously. The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×50 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 30% B to 70% B in 10 min; Detector: UV 254, 220 nm) to afford the title compound as a pink solid (48.6 mg, 46% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.13 (br s, 1H), 9.02 (s, 1H), 8.51 (s, 1H), 7.55-7.28 (m, 10H), 6.81-6.79 (d, 2H), 5.02-4.94 (m, 2H), 4.58-4.54 (d, 1H), 4.26-4.22 (d, 1H), 3.71-3.65 (m, 4H). MS: (ES, m/z): 434 [M+H]<sup>+</sup>.

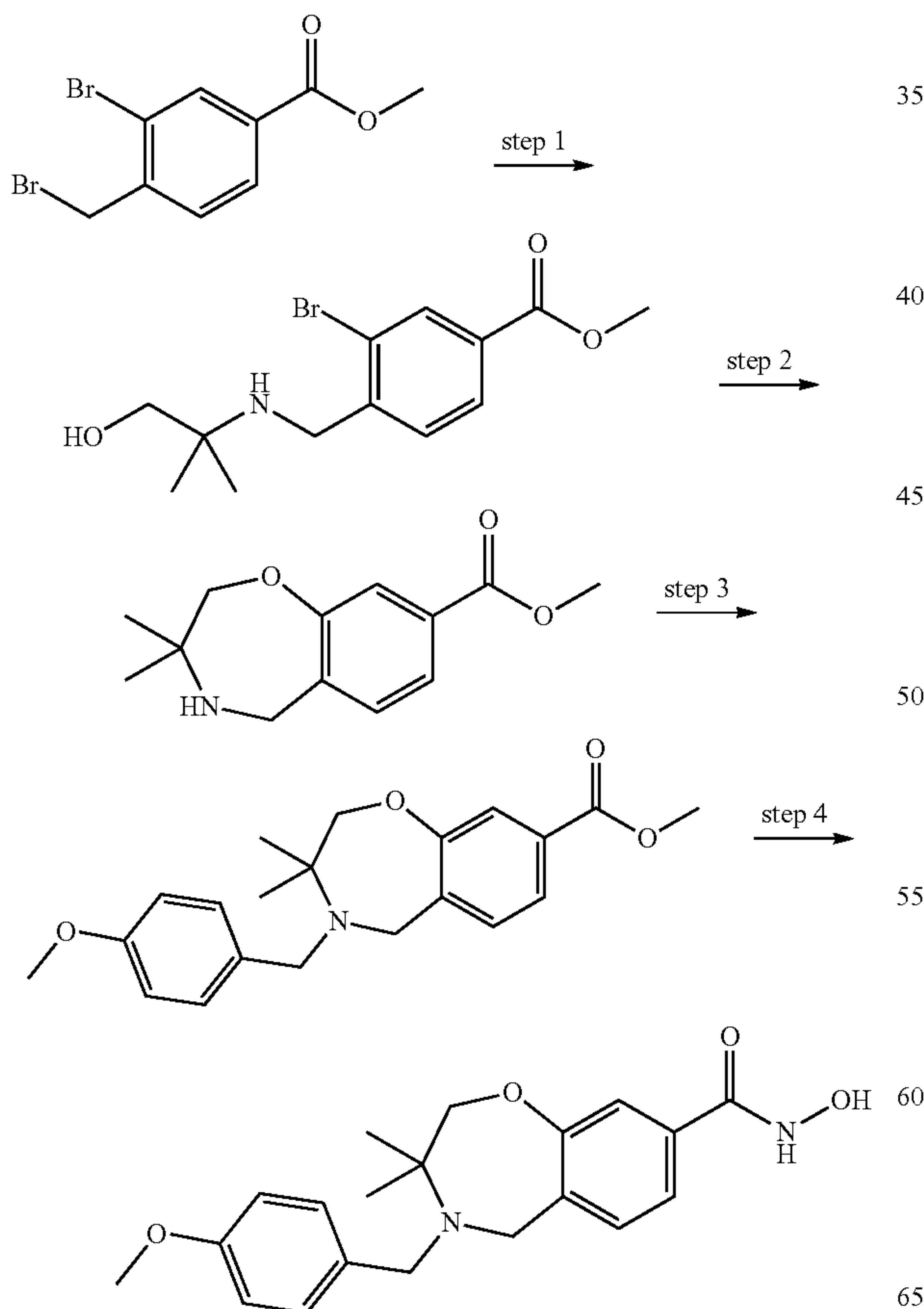


TABLE 7

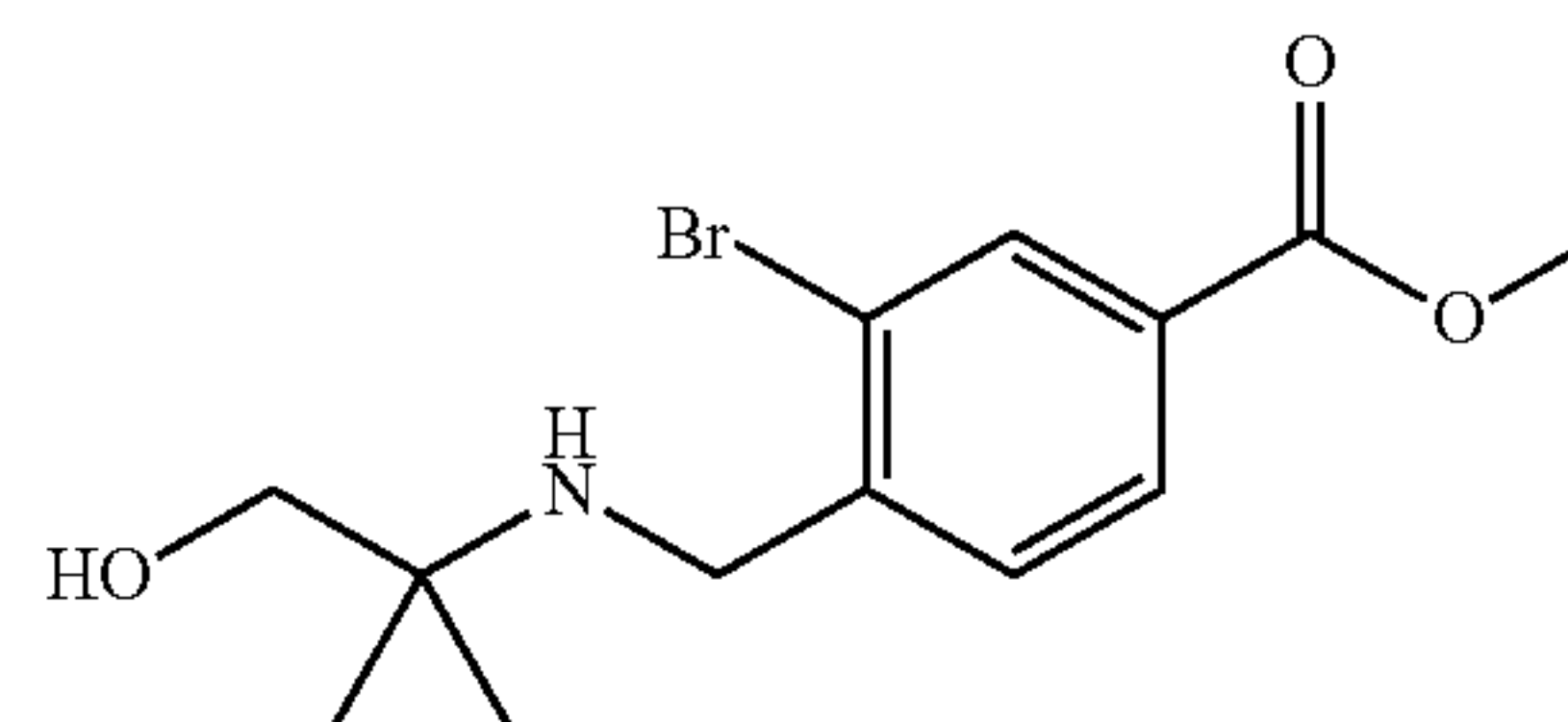
The following compounds were prepared according to the method of Example 25, using (S)-2-amino-1-phenylethan-1-ol.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 434 [M + H] <sup>+</sup>	11.12 (s, 1H), 9.02 (s, 1H), 8.51 (s, 1H), 7.57-7.51 (m, 3H), 7.51-7.43 (m, 3H), 7.42-7.33 (m, 2H), 7.32-7.26 (m, 2H), 6.81-6.79 (d, J = 8.8 Hz, 2H), 5.02-4.94 (m, 2H), 4.58-4.54 (d, J = 15.6 Hz, 1H), 4.23-4.22 (d, J = 14.0 Hz, 1H), 3.71-3.64 (m, 4H)

## Example 26

Preparation of N-hydroxy-4-(4-methoxybenzyl)-3,3-dimethyl-2,3,4,5-tetrahydrobenzo [f][1,4]oxazepine-8-carboxamide

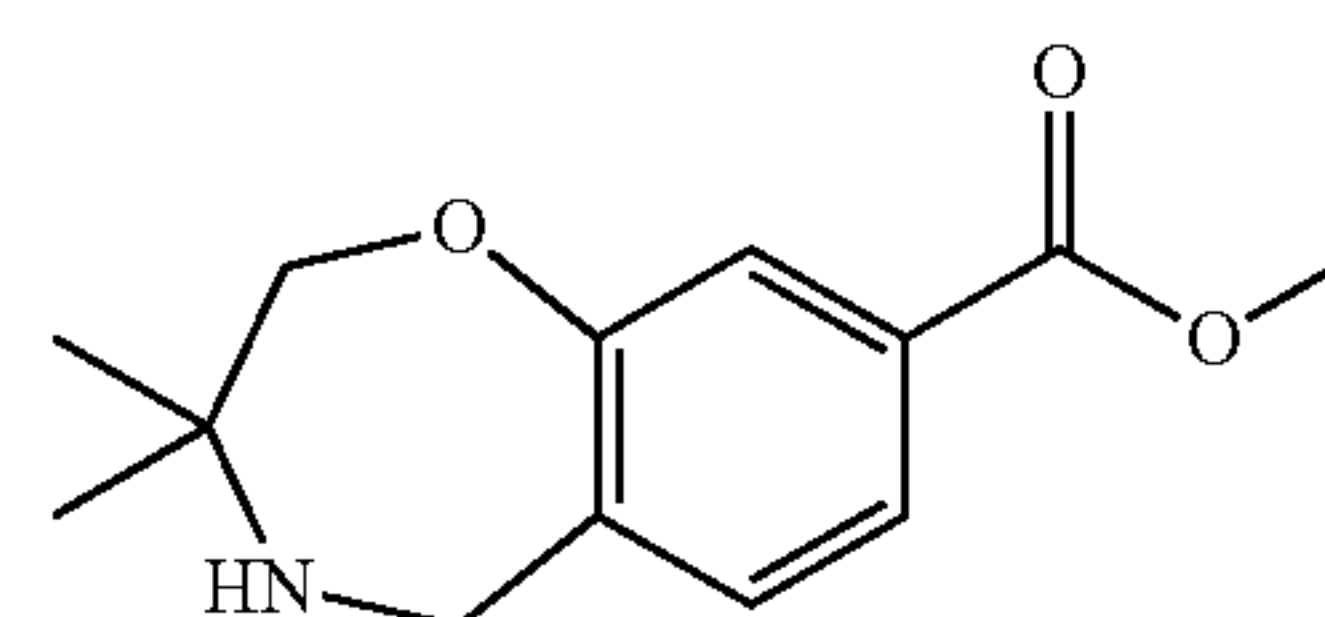


Step-1: Methyl 3-bromo-4-[(1-hydroxy-2-methylpropan-2-yl)amino]methyl]benzoate



Into a 500-mL round-bottom flask, were placed a solution of 2-amino-2-methylpropan-1-ol (11.52 g, 129.24 mmol, 2 equiv) in MeCN (150 mL), K<sub>2</sub>CO<sub>3</sub> (13.40 g, 97.10 mmol, 1.5 equiv). This was followed by the addition of a solution of methyl 3-bromo-4-(bromomethyl)benzoate (20 g, 64.94 mmol, 1 equiv) in MeCN (50 mL) dropwise with stirring at room temperature. The resulting solution was stirred for 16 h at room temperature, then concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (200 mL). The resulting solution was extracted with EtOAc (3×200 mL) and the organic layers combined, washed with H<sub>2</sub>O (3×200 mL), and concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:4) to afford the title compound as an off-white solid (8.7 g, 42% yield). MS: (ES, m/z): 316 [M+H]<sup>+</sup>.

Step 2: Methyl 3,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



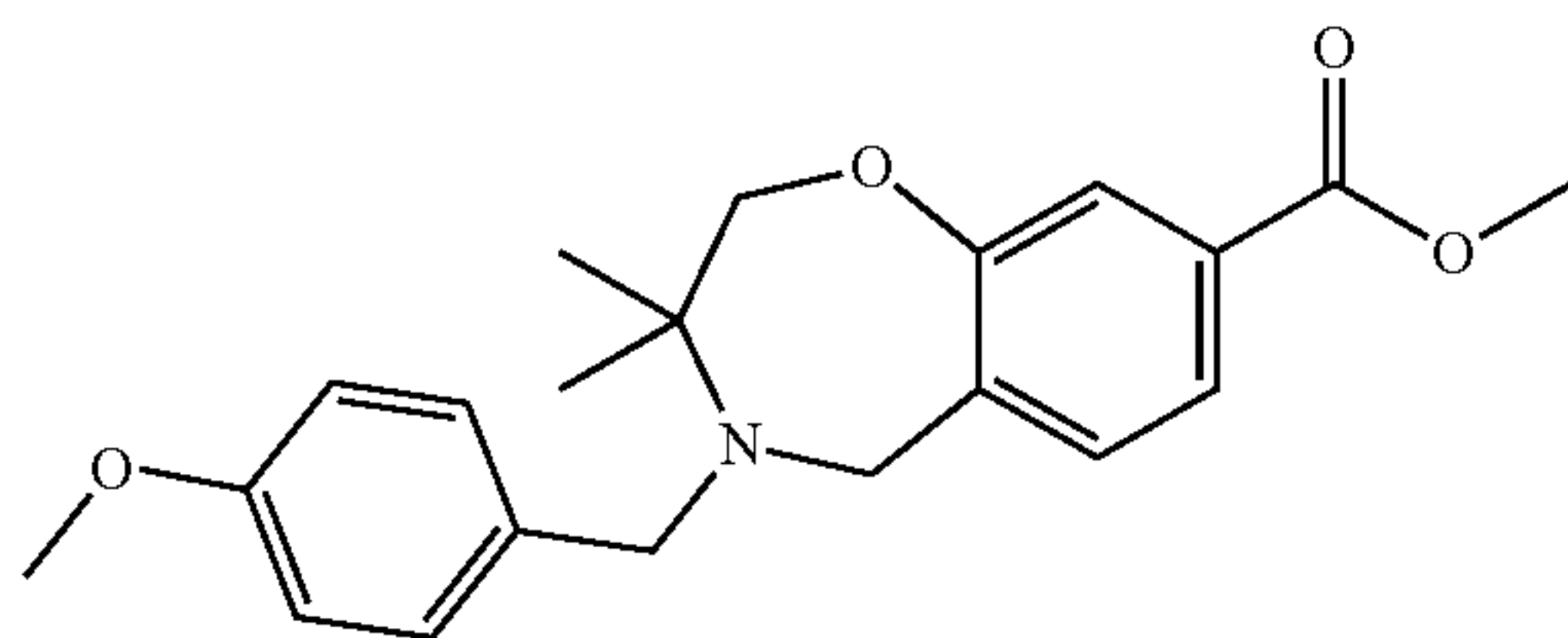
Into a 250-mL pressure reactor purged and maintained with an inert atmosphere of nitrogen, were placed a



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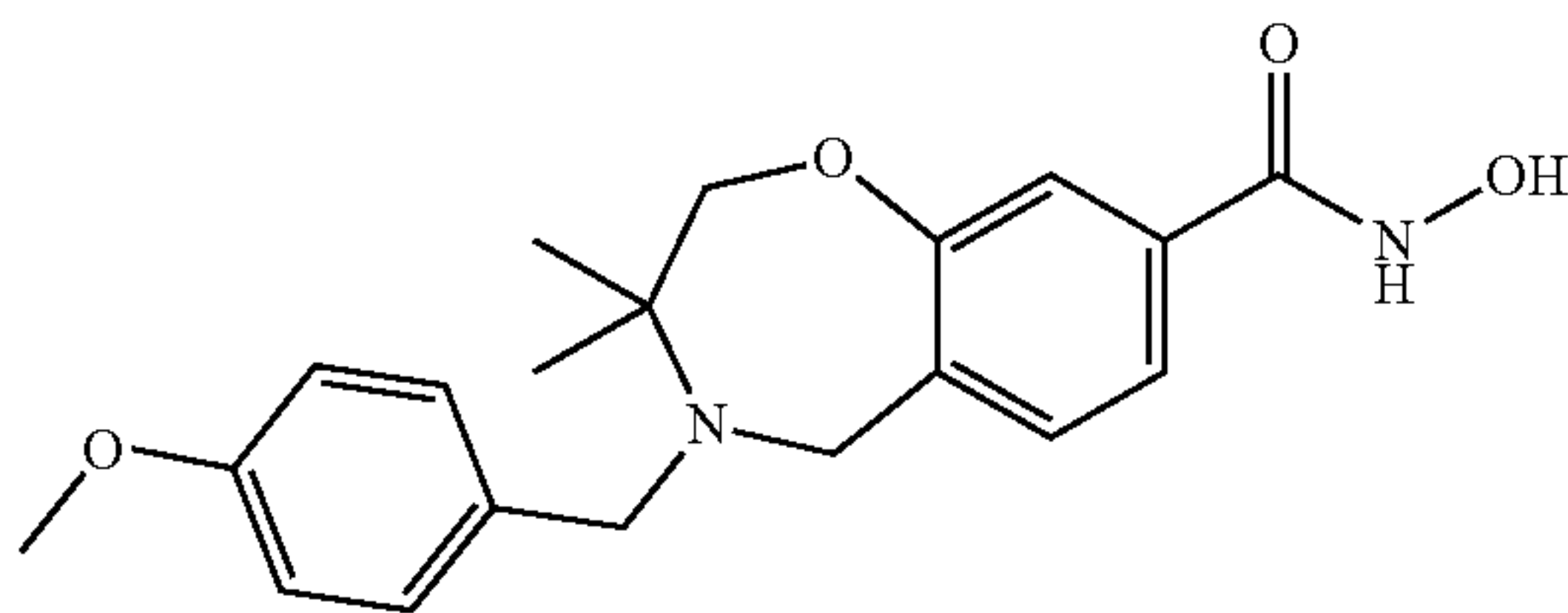
solution of methyl 3-bromo-4-[[1-(1-hydroxy-2-methylpropan-2-yl)amino]methyl]benzoate (8.7 g, 27.52 mmol, 1 equiv) in isopropanol (150 mL),  $K_2CO_3$  (5.7 g, 41.30 mmol, 1.5 equiv) and CuI (1.57 g, 8.26 mmol, 0.3 equiv). The resulting solution was stirred overnight at 110° C. in an oil bath, then concentrated under vacuum. The residue was diluted with  $H_2O$  (200 mL). The resulting solution was extracted with EtOAc (3×200 mL) and the combined organic layers was washed with  $H_2O$  (3×200 mL) and concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:2) to afford the title compound as a green oil (3.9 g, 60% yield).  $^1H$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$ (ppm): 7.63-7.60 (d,  $J$ =12.8 Hz, 1H), 7.54-7.52 (s, 1H), 7.25-7.23 (d,  $J$ =7.6 Hz, 1H), 4.01 (s, 2H), 3.94-3.89 (m, 5H), 1.23 (s, 6H). MS: (ES,  $m/z$ ): 236  $[M+H]^+$ .

Step-3: Methyl 4-(4-methoxybenzyl)-3,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed a solution of methyl 3,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.43 mmol, 1 equiv) in THF (2 mL). This was followed by the addition of sodium hydride (60%, 51 mg, 2.12 mmol, 3 equiv). To this was added 1-(bromomethyl)-4-methoxybenzene (86 mg, 0.43 mmol, 1 equiv). The resulting solution was stirred for 22 h at room temperature. The reaction was then quenched with water (3 mL). The resulting solution was extracted with EtOAc (3×10 mL), washed with water (3×10 mL) and concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:4) to afford the title compound as a light yellow oil (100 mg, 66% yield). MS: (ES,  $m/z$ ): 356  $[M+H]^+$ .

Step-4: N-Hydroxy-4-(4-methoxybenzyl)-3,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



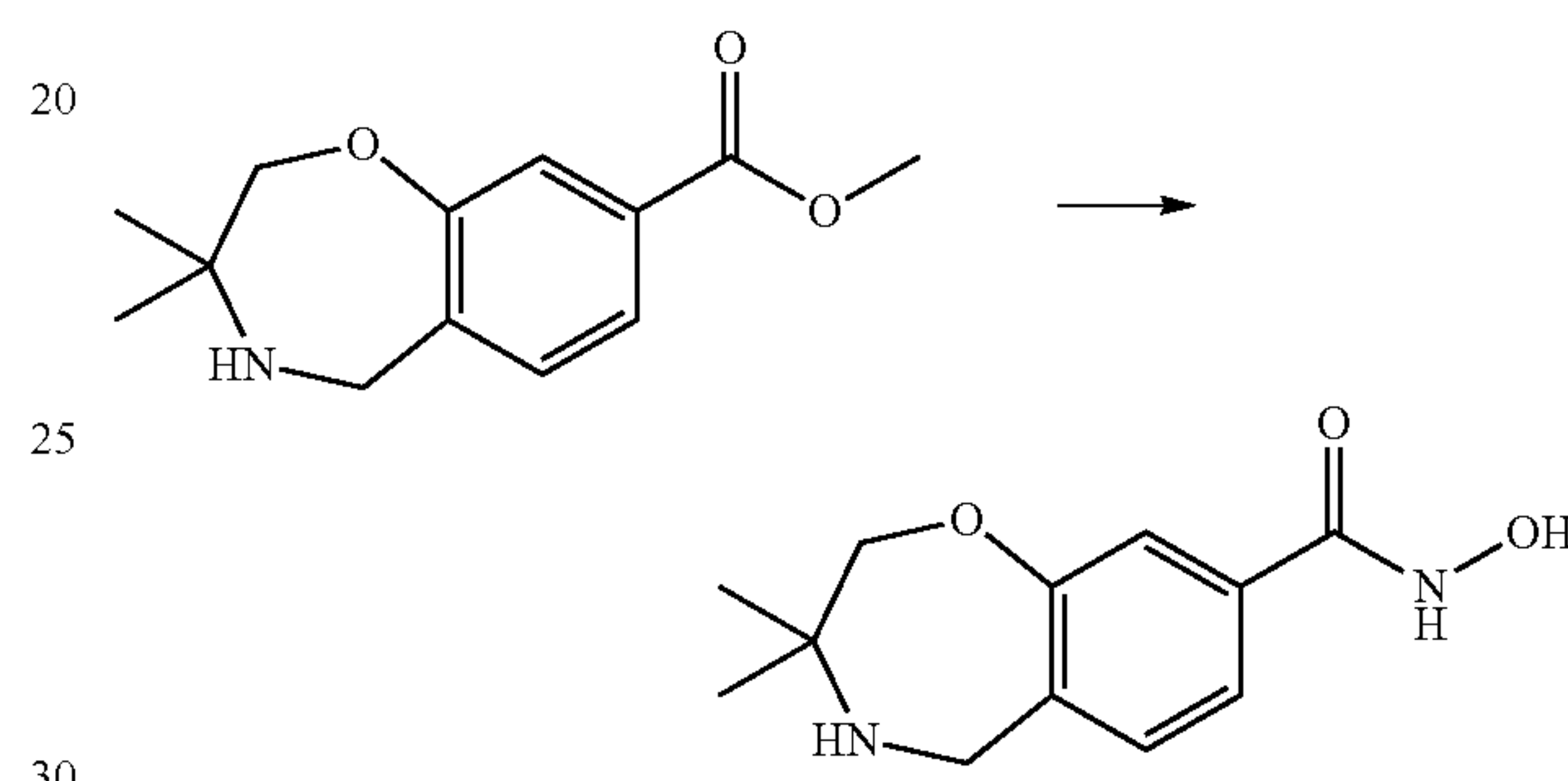
Into a 8-mL vial, was placed a solution of methyl 4-(4-methoxybenzyl)-3,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.28 mmol, 1 equiv) in THF/MeOH (4:1, 2.5 mL). This was followed by the addition of  $NH_2OH$  (50% in water, 0.56 mL, 30 equiv). To this was added aq. 1N NaOH (0.55 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude

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product was purified by Prep-HPLC (Column: XBridge C18 OBD, 5  $\mu m$ , 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 20 mL/min; Gradient: 30% B to 70% B in 10 min; Detector: UV 254, 220 nm) to afford the title compound as a TFA salt as a light pink solid (27 mg, 20% yield).  $^1H$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$ (ppm): 11.30 (s, 1H), 9.80 (s, 1H), 9.52-8.61 (br, 1H), 7.47-7.39 (m, 4H), 7.29-7.03 (m, 3H), 5.02-4.51 (m, 2H), 4.51-4.16 (m, 3H) 4.32-4.28 (m, 3H) 3.60-3.45 (m, 1H), 1.75-1.41 (m, 6H). MS: (ES,  $m/z$ ): 357  $[M+H]^+$ .

### Example 27

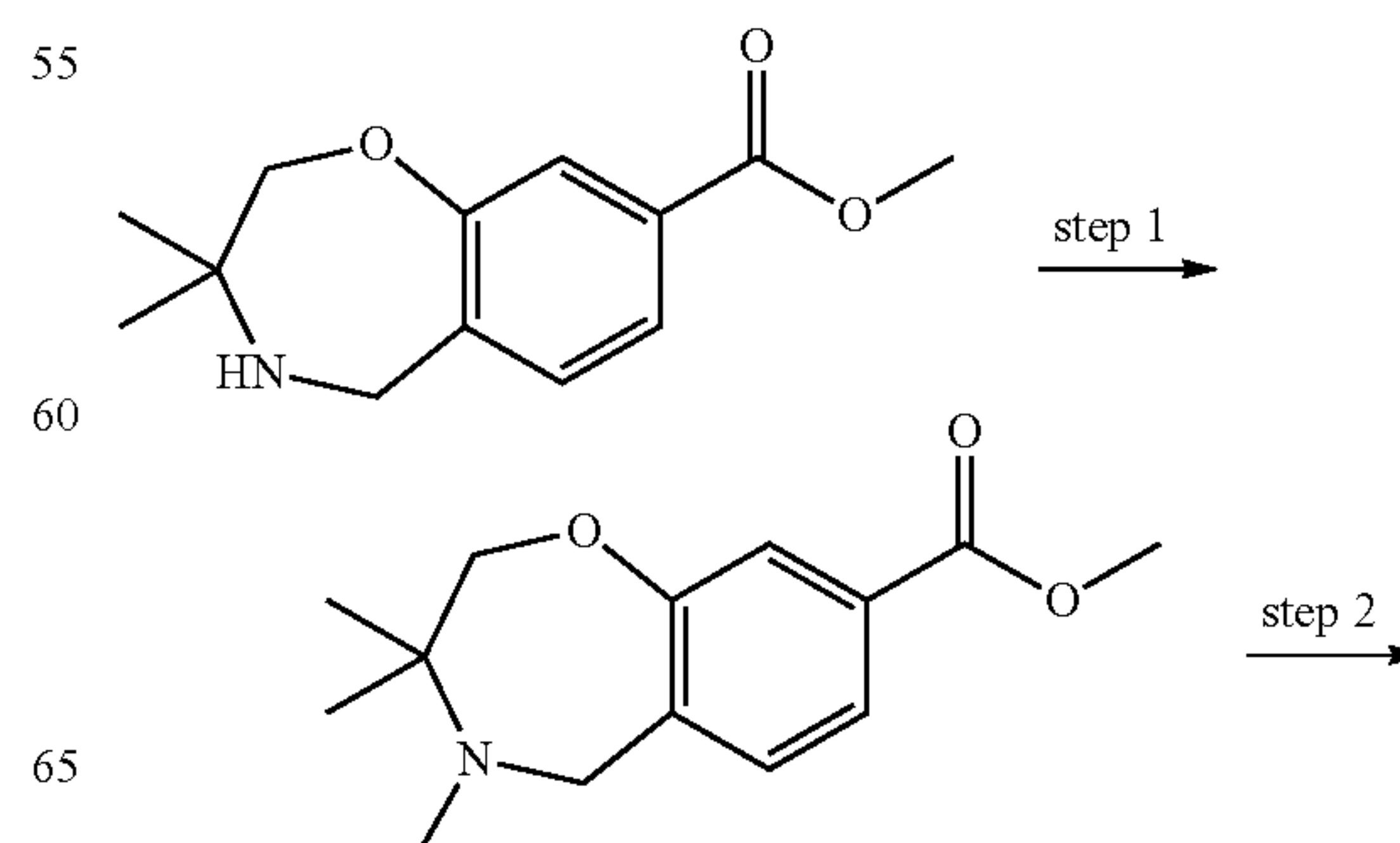
Preparation of N-hydroxy-3,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed a solution of methyl 3,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.43 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), followed by the addition of aq. 1N NaOH (0.85 mL, 2 equiv) and  $NH_2OH$  (50% in  $H_2O$ , 0.84 mL, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5  $\mu m$ , 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 2% B to 8% B in 7 min; Detector: UV 254, 220 nm) to afford the title compound as the TFA salt as an off-white solid (57 mg, 39% yield).  $^1H$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$ (ppm): 11.30 (br, 1H), 9.32 (m, 2H), 9.12 (br, 1H), 7.51 (s, 2H), 7.42 (s, 1H), 4.42 (s, 2H), 4.03 (s, 2H), 1.39 (s, 6H) MS: (ES,  $m/z$ ): 237  $[M+H]^+$ .

### Example 28

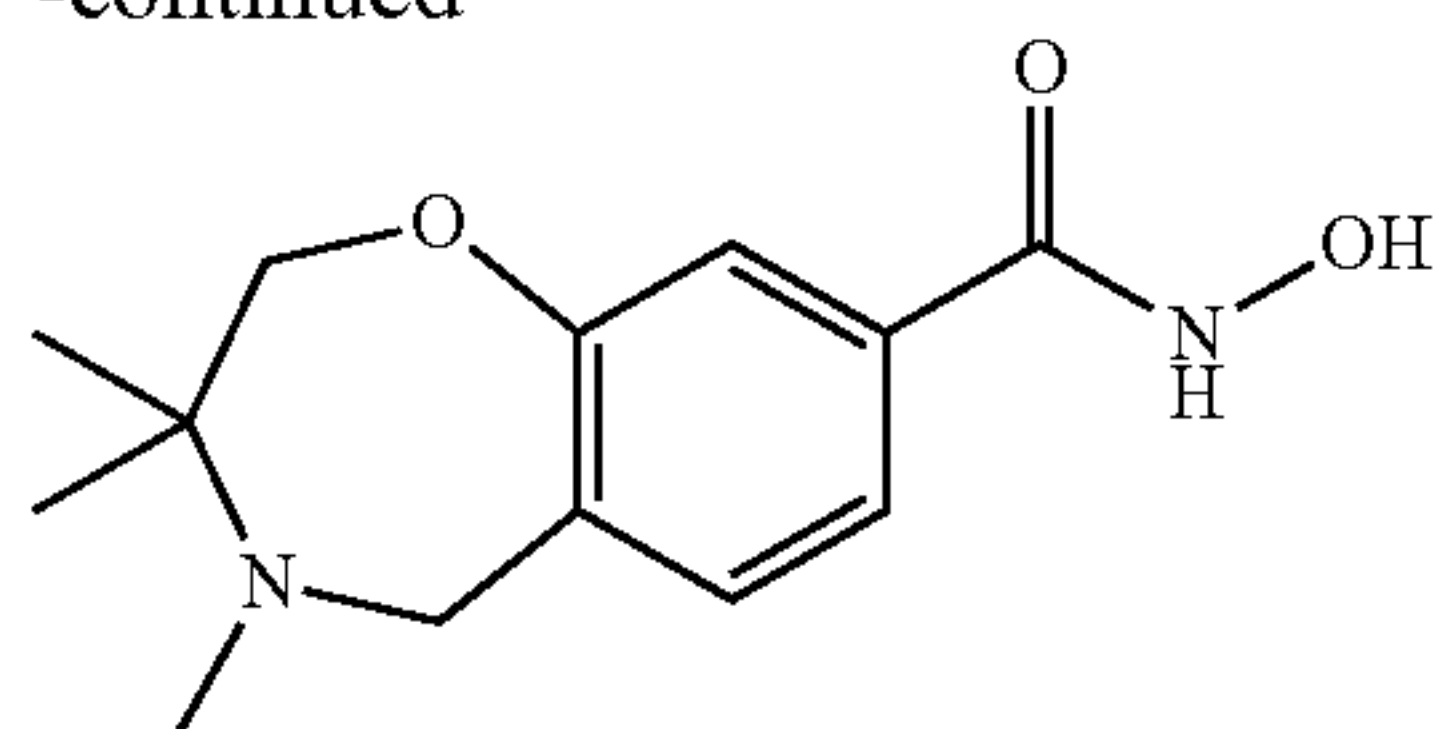
Preparation of N-hydroxy-3,3,4-trimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



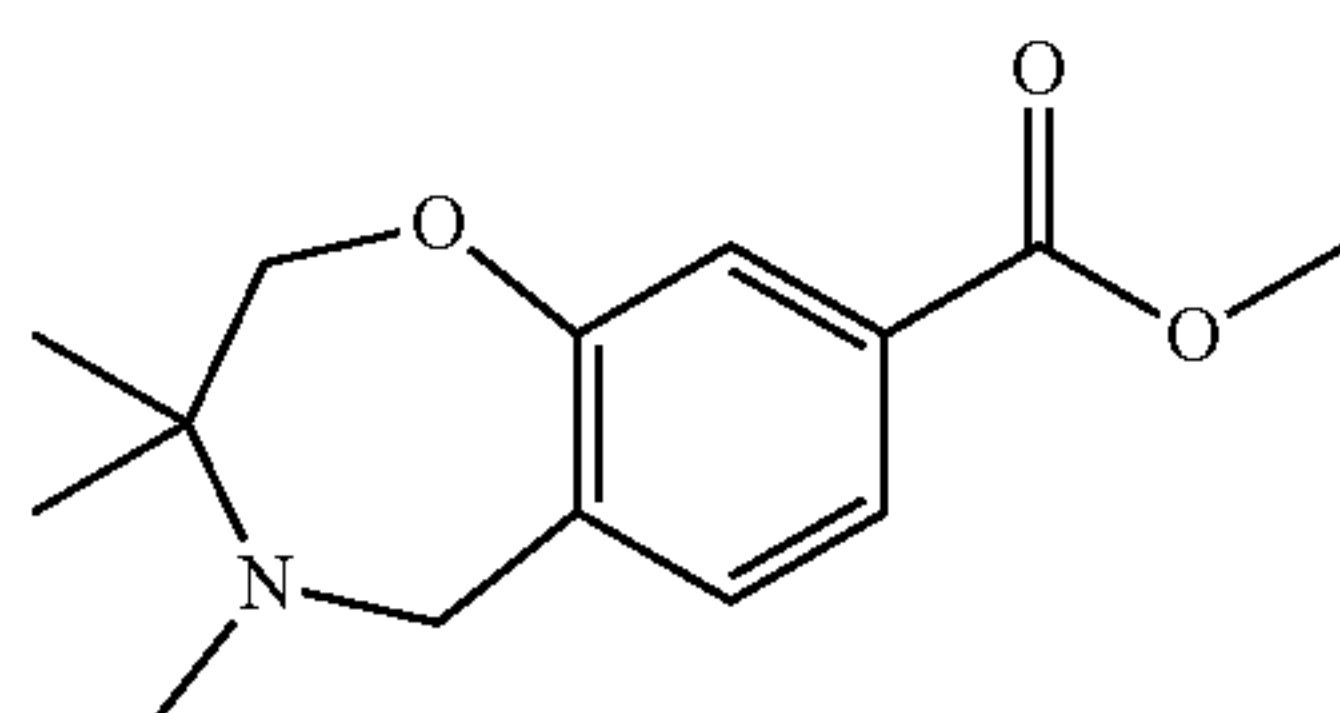


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-continued

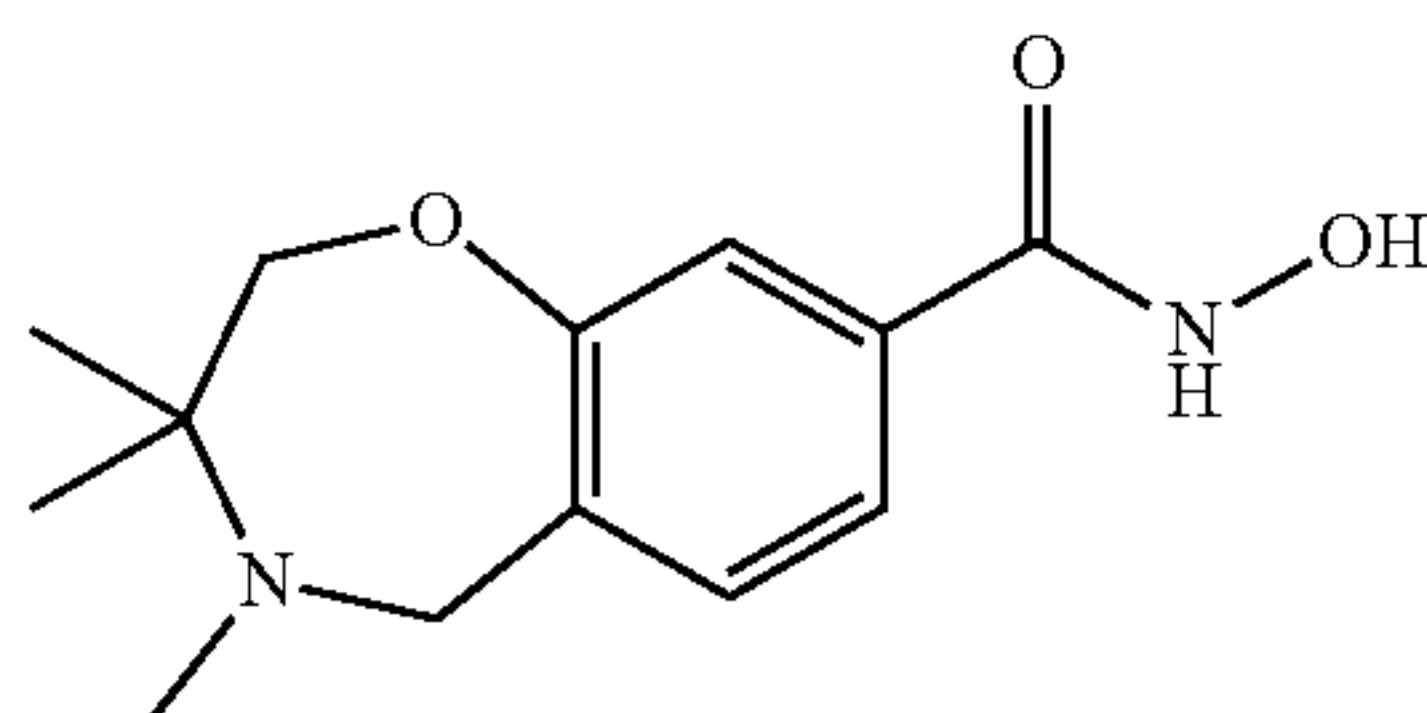


Step-1: Methyl 3,3,4-trimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed a solution of methyl 3,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.43 mmol, 1 equiv) in acetic acid (2 mL). This was followed by the addition of formaldehyde (38 mg, 1.27 mmol, 3 equiv) and NaBH(OAc)<sub>3</sub> (449 mg, 2.13 mmol, 5 equiv). The resulting mixture was stirred for 16 h at room temperature. H<sub>2</sub>O (20 mL) was added, then the resulting solution was extracted with EtOAc (3×30 mL), washed with H<sub>2</sub>O (3×20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a yellow oil (28 mg, 27% yield). MS: (ES, m/z): 250 [M+H]<sup>+</sup>.

Step-2: N-Hydroxy-3,3,4-trimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

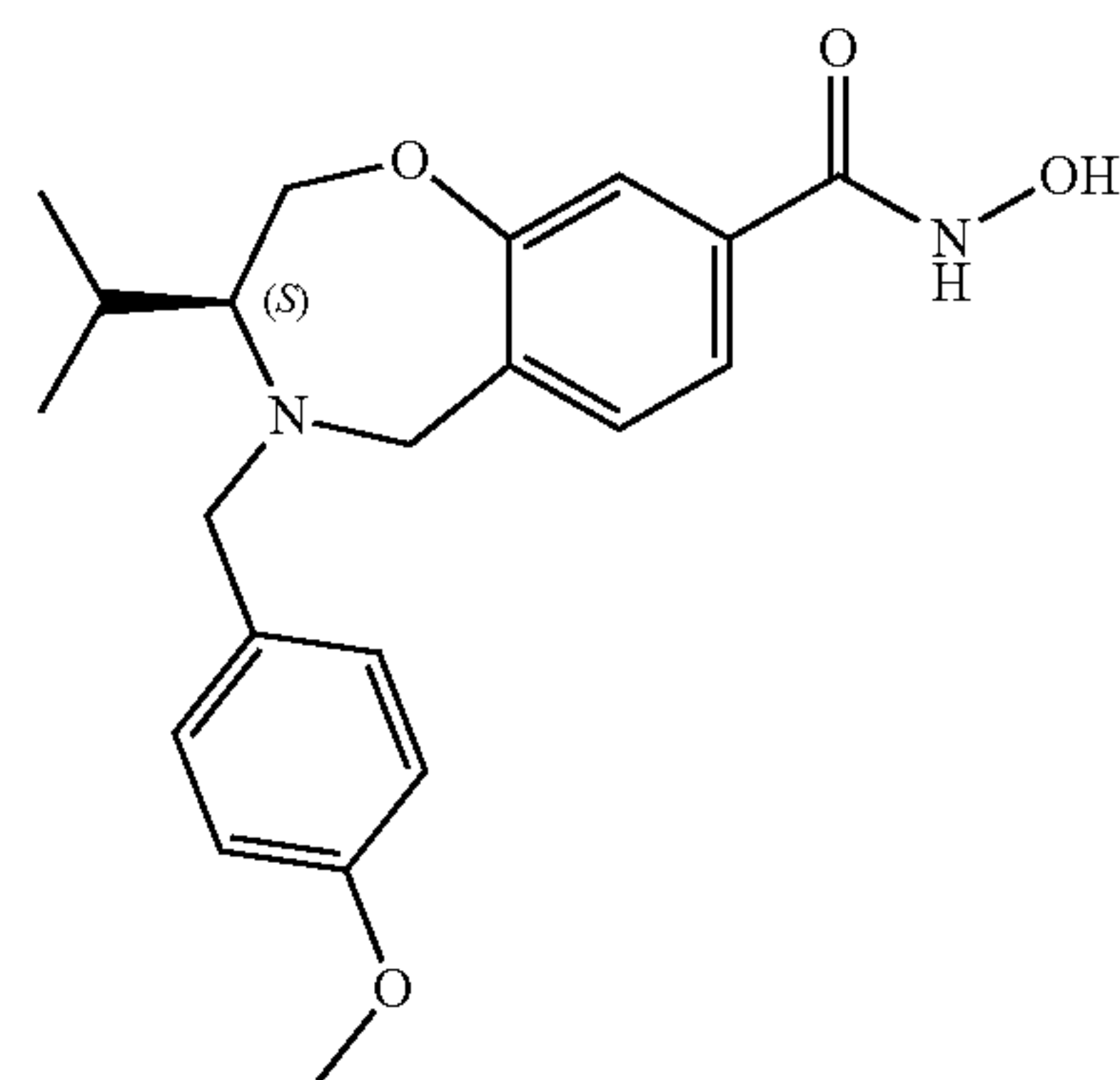
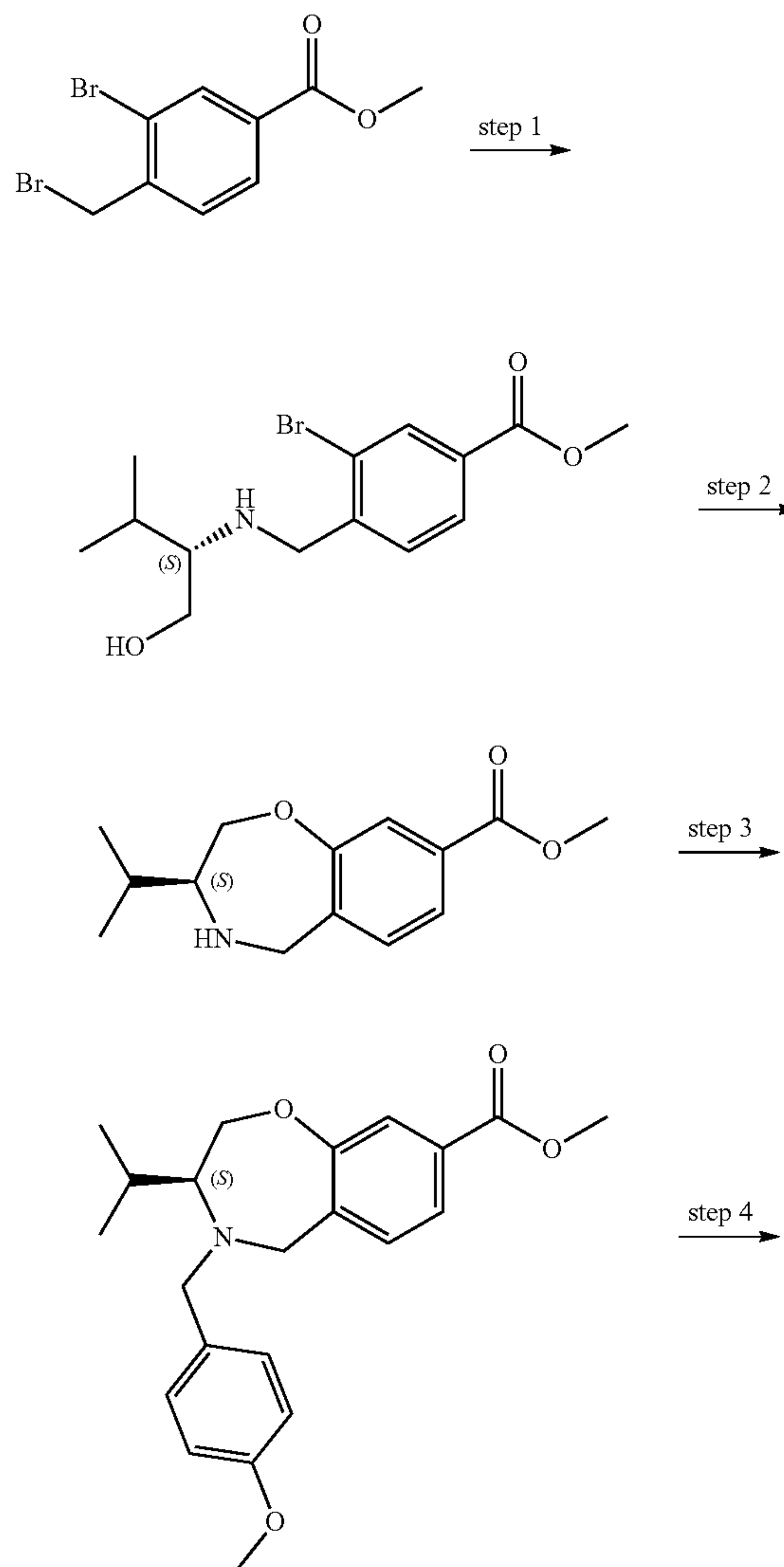


Into a 8-mL vial, was placed a solution of methyl 3,3,4-trimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (28.4 mg, 0.11 mmol, 1 equiv) in THF/MeOH (4:1, 1 mL), followed by aq. 1N NaOH (0.23 mL, 2 equiv) and NH<sub>2</sub>OH (50% in H<sub>2</sub>O, 0.23 mL, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge RP C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 5% B to 13% B in 4 min; Detector: UV 254, 220 nm) to afford the title compound as the TFA salt as a brown oil (18 mg, 44% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.30 (br s, 1H), 10.17-10.08 (br s, 1H), 9.12 (br, 1H), 7.53-7.41 (m, 3H), 4.74-4.70 (d, J=12.0 Hz, 1H), 4.50-4.28 (m, 2H), 4.07-4.03 (d, J=12.0 Hz, 1H), 2.77-2.73 (s, 3H), 1.53 (s, 3H), 1.40 (s, 3H). MS: (ES, m/z): 251 [M+H]<sup>+</sup>.

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Example 29

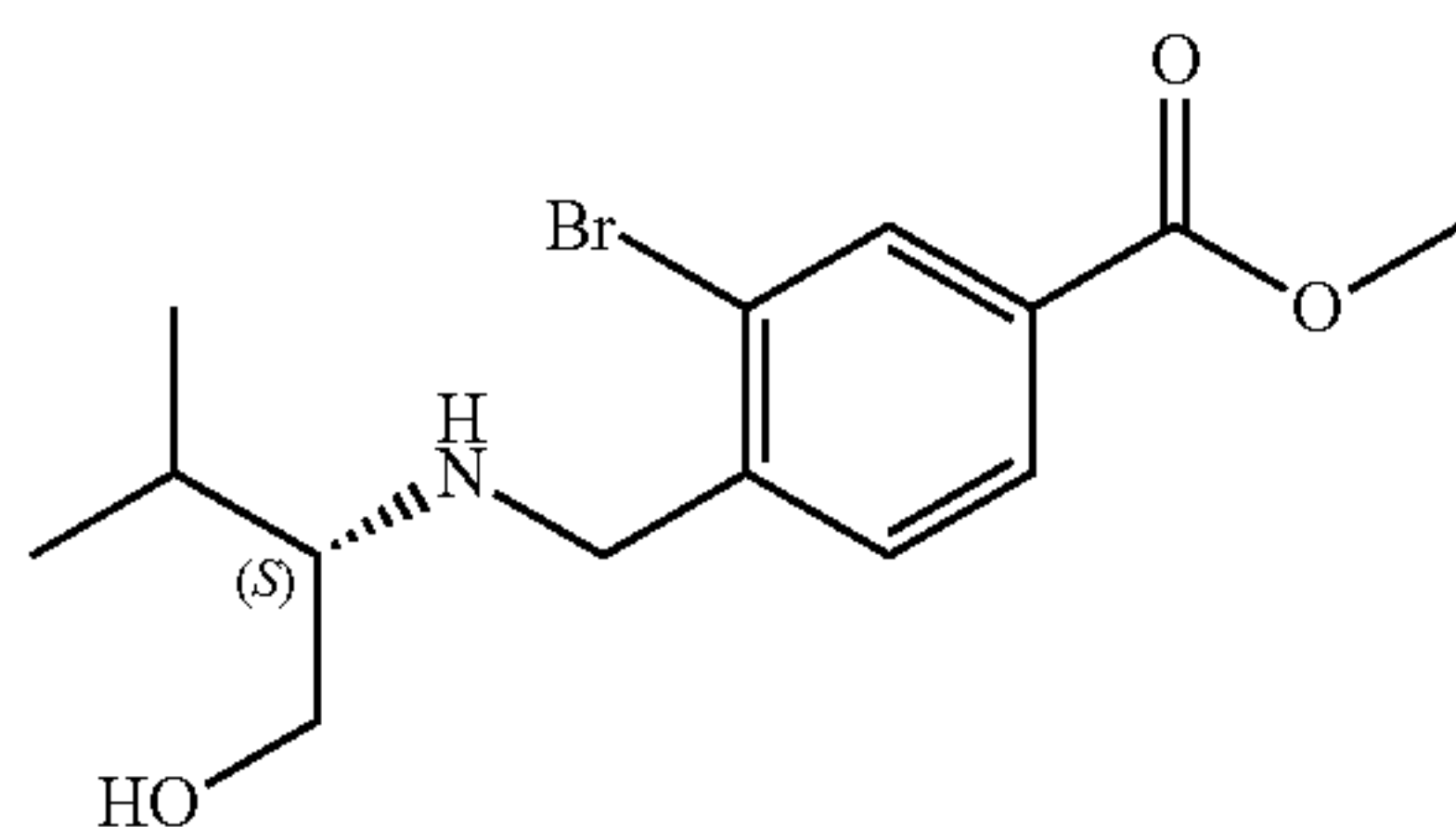
Preparation of (S)—N-hydroxy-3-isopropyl-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide





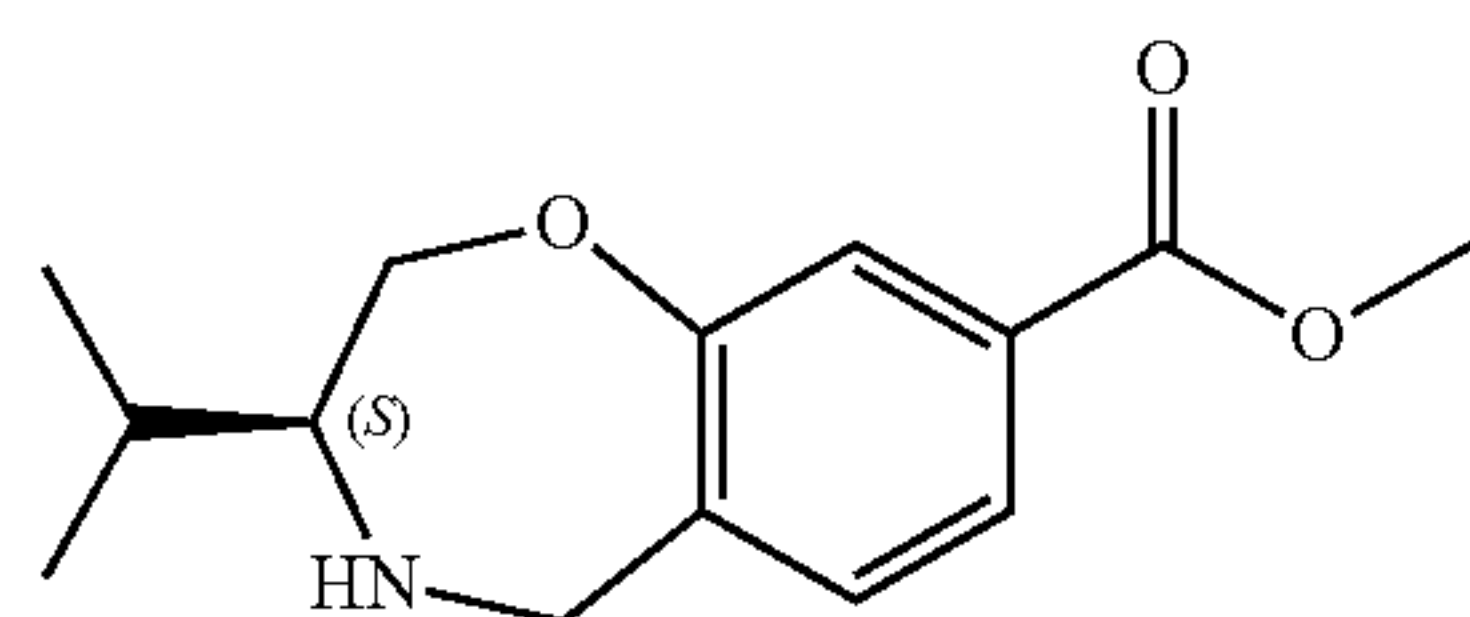
97

Step-1: Methyl (S)-3-bromo-4-(((1-hydroxy-3-methylbutan-2-yl)amino)methyl)benzoate



Into a 1-L round-bottom flask, was placed a solution of (S)-2-amino-3-methylbutan-1-ol (23.33 g, 226.15 mmol, 2 equiv) in MeCN (300 mL). This was followed by the addition of a solution of methyl 3-bromo-4-(bromomethyl)benzoate (35 g, 113.65 mmol, 1 equiv) in MeCN (200 mL) dropwise with stirring. The resulting solution was stirred for 17 h at room temperature, then concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (300 mL), extracted with EtOAc (3×300 mL) and the combined organic layers were concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:2) to afford the title compound as an off-white solid (20 g, 53% yield). MS: (ES, m/z): 330 [M+H]<sup>+</sup>.

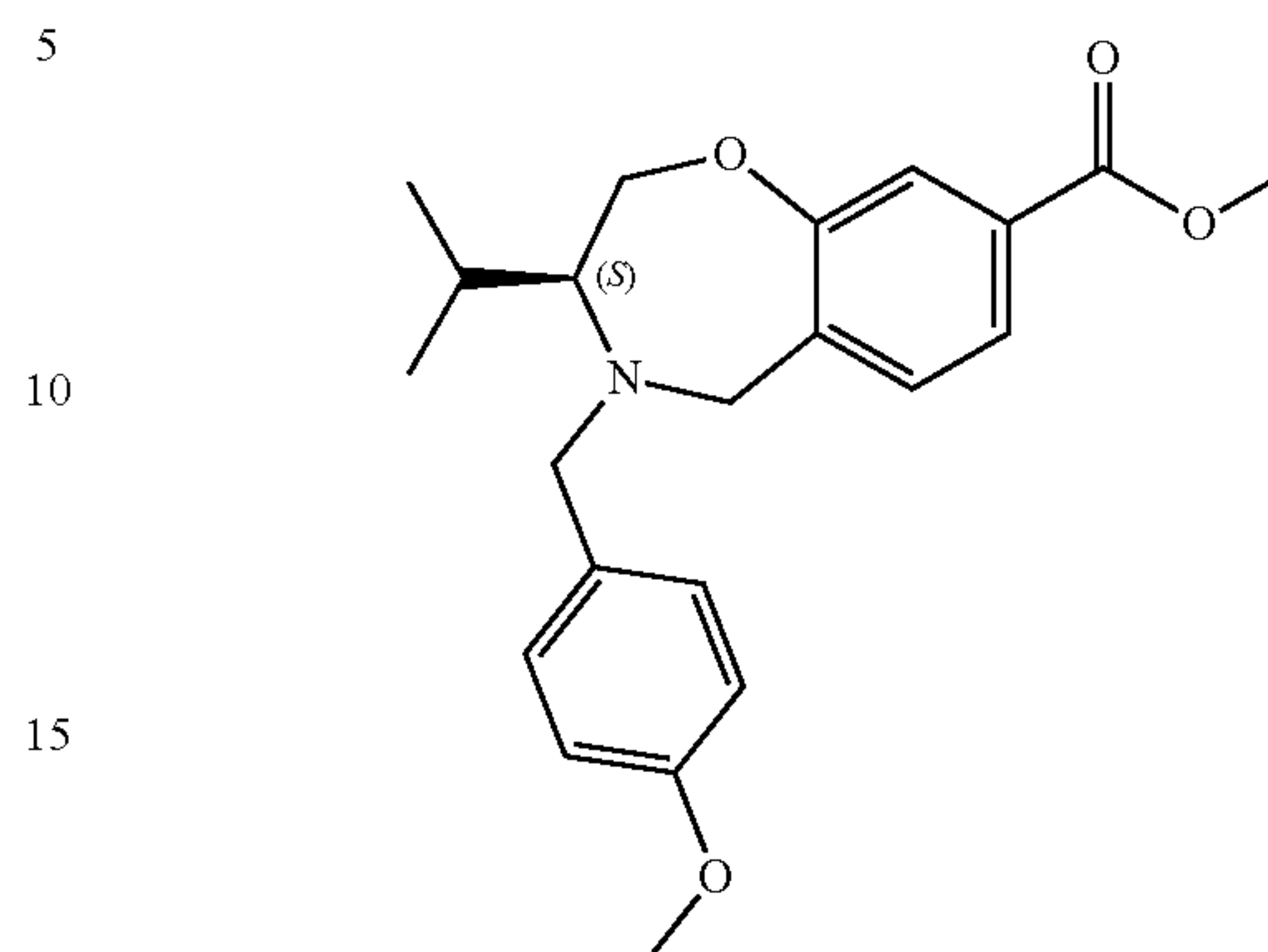
Step-2: Methyl (S)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 500-mL pressure tank reactor purged and maintained with an inert atmosphere of nitrogen, were placed a solution of methyl (S)-3-bromo-4-(((1-hydroxy-3-methylbutan-2-yl)amino)methyl)benzoate (20 g, 60.57 mmol, 1 equiv) in isopropanol (350 mL), K<sub>2</sub>CO<sub>3</sub> (12.9 g, 93.48, 1.5 equiv) and CuI (3.6 g, 18.95 mmol, 0.3 equiv). The resulting mixture was stirred for 23 h at 110° C. in an oil bath and then concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (300 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×300 mL). The combined organic layers were washed with H<sub>2</sub>O (3×300 mL) and concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a yellow oil (5.3 g, 35% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 7.66-7.64 (d, J=8.0 Hz, 1H), 7.57 (s, 1H), 7.31-7.29 (d, J=8.0 Hz, 1H), 4.43-4.40 (m, 1H), 4.09-3.95 (m, 2H), 3.94-3.81 (s 3H), 3.72-3.69 (m, 1H), 2.89-2.86 (m, 1H), 1.88-1.80 (m, 1H), 1.03-0.99 (m, 6H). MS: (ES, m/z): 250 [M+H]<sup>+</sup>.

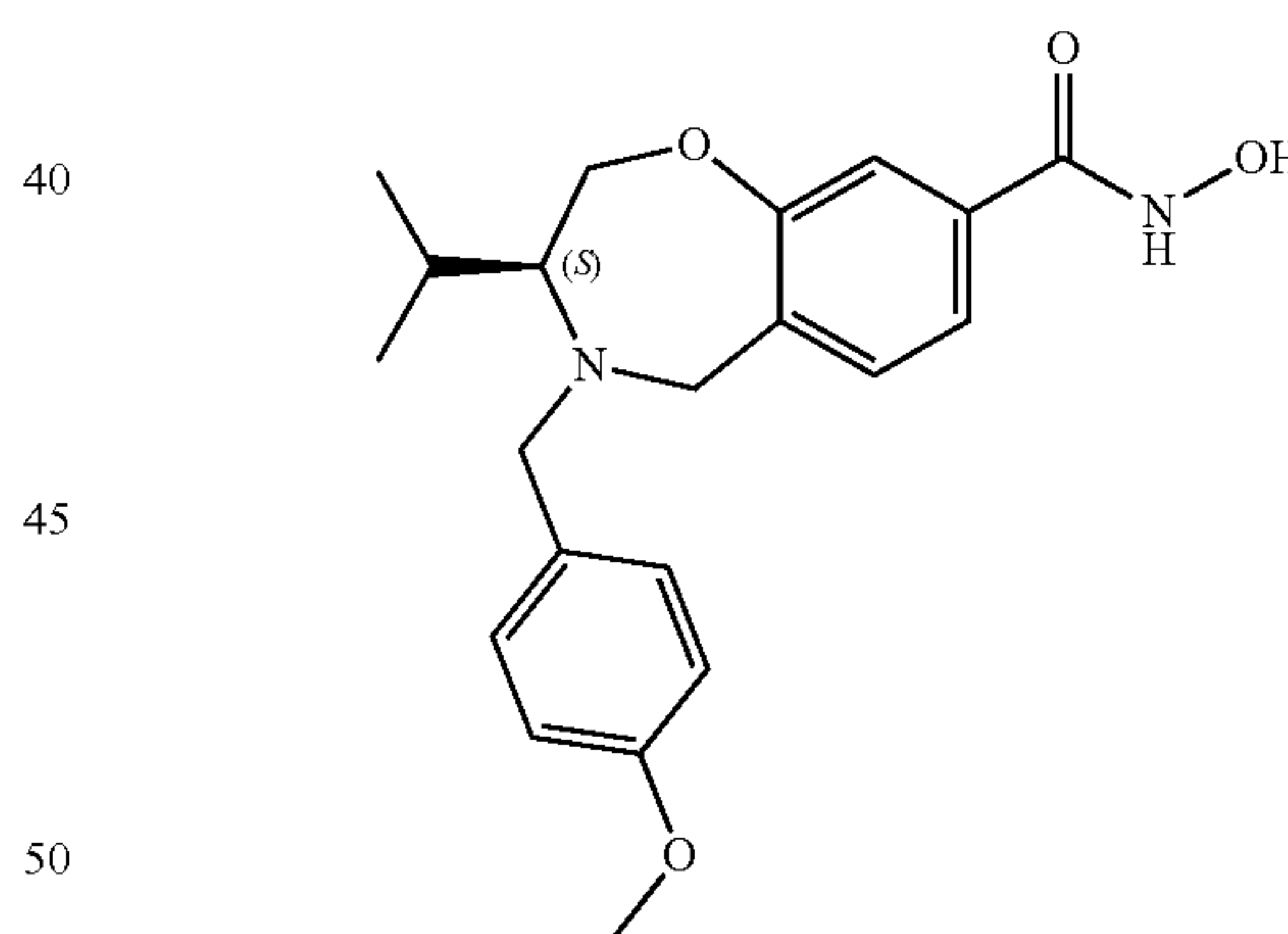
98

Step-3: Methyl (S)-3-isopropyl-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed a solution of methyl (S)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.40 mmol, 1 equiv) in THF (2 mL), followed by the addition of sodium hydride (60% dispersion in oil, 49 mg, 2.04 mmol, 3 equiv) at 0° C. To this was added 1-(bromomethyl)-4-methoxybenzene (81 mg, 0.40 mmol, 1 equiv). The resulting solution was stirred for 16 h at room temperature, then quenched with water (3 mL). The resulting mixture was concentrated under vacuum and diluted with H<sub>2</sub>O (10 mL). The resulting solution was extracted with EtOAc (3×10 mL), washed with H<sub>2</sub>O (3×10 mL), and concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:4) to afford the title compound as a yellow oil (70 mg, 47% yield). MS: (ES, m/z): 370 [M+H]<sup>+</sup>.

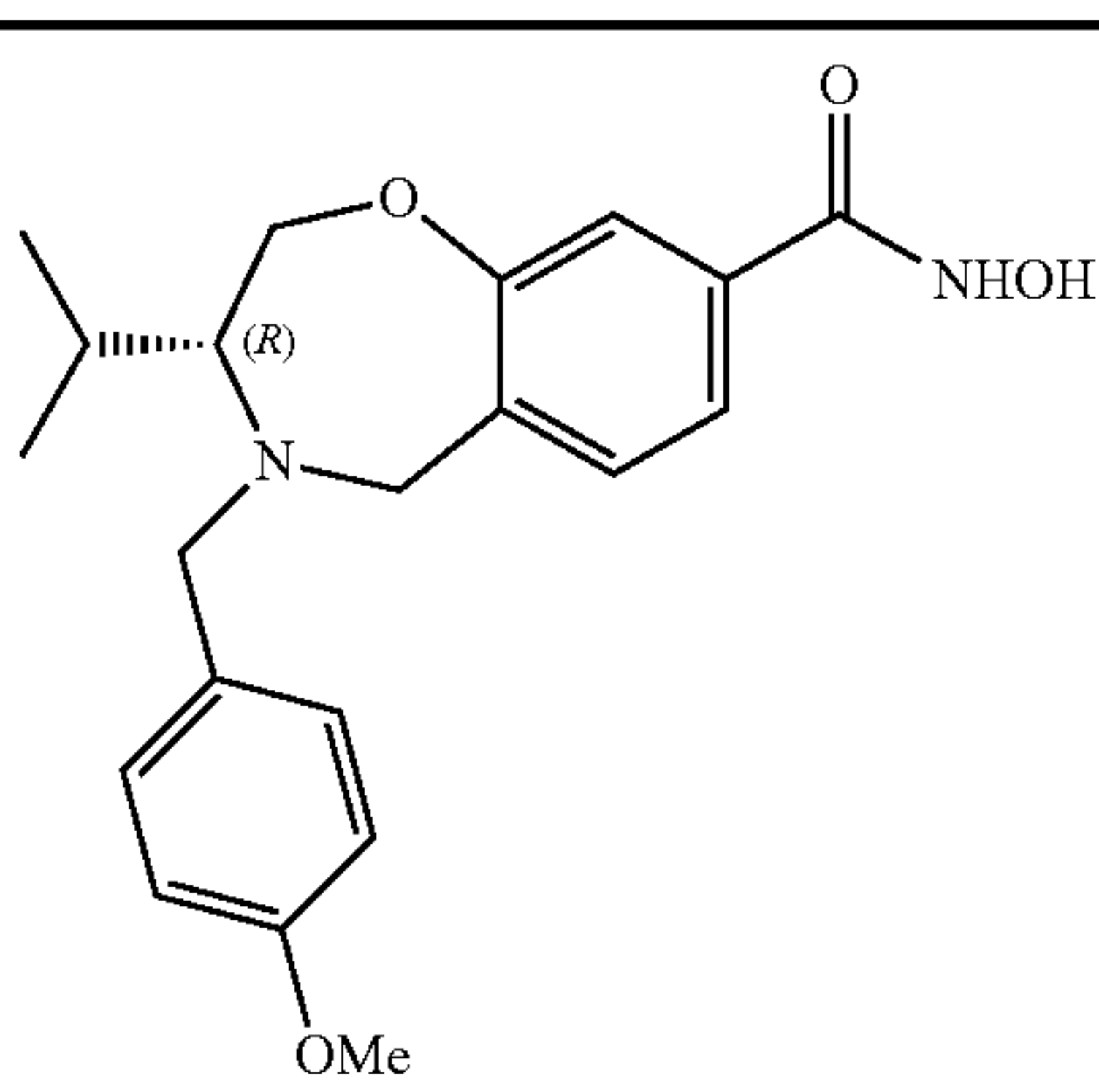
Step-4: (S)—N-hydroxy-3-isopropyl-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed a solution of methyl (S)-3-isopropyl-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (70 mg, 0.19 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), followed by the addition of NH<sub>2</sub>OH (50% in water, 0.38 mL, 30 equiv) and aq. 1N NaOH (0.38 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 20 mL/min; Gradient: 5% B to 70% B in 7 min; Detector: UV 254, 220 nm) to afford the title compound as the TFA salt as a light brown solid (42 mg, 48% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.40-10.89 (s, 1H), 9.44-8.65 (br, 1H), 7.50-6.68 (m, 7H), 4.98-3.89 (m, 7H), 3.75-3.71 (m, 3H), 2.21-1.91 (s, 1H), 1.09-0.89 (s, J=6.4 Hz, 6H). MS: (ES, m/z): 371 [M+H]<sup>+</sup>.



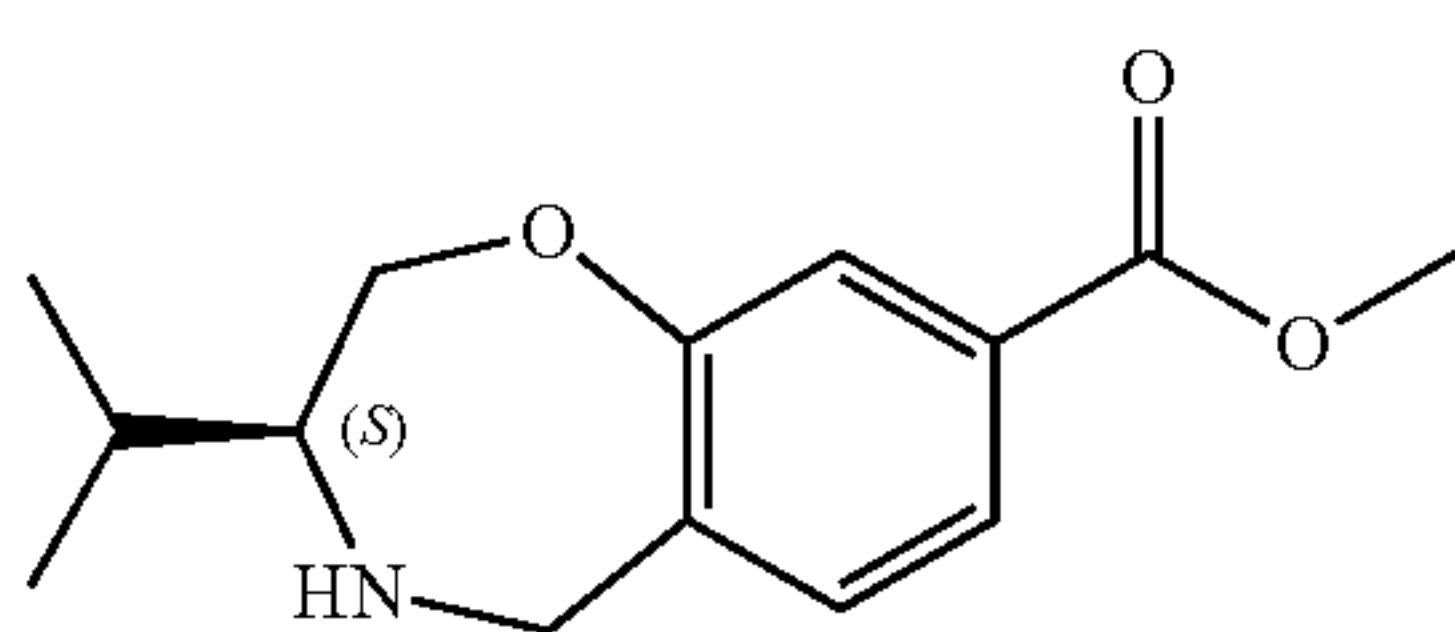
TABLE 8

The following compound was prepared according to the method of Example 29, using (R)-2-amino-3-methylbutan-1-ol.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 371 [M + H] <sup>+</sup>	11.51-10.85 (br, 1H), 9.71-8.92 (br, 1H), 7.51-7.22 (m, 3H), 7.19-6.79 (m, 4H), 4.99-4.09 (m, 5H), 3.86-3.67 (m, 3H), 2.27-1.71 (m, 1H), 1.21-0.56 (d, J = 6.0 Hz, 6H)

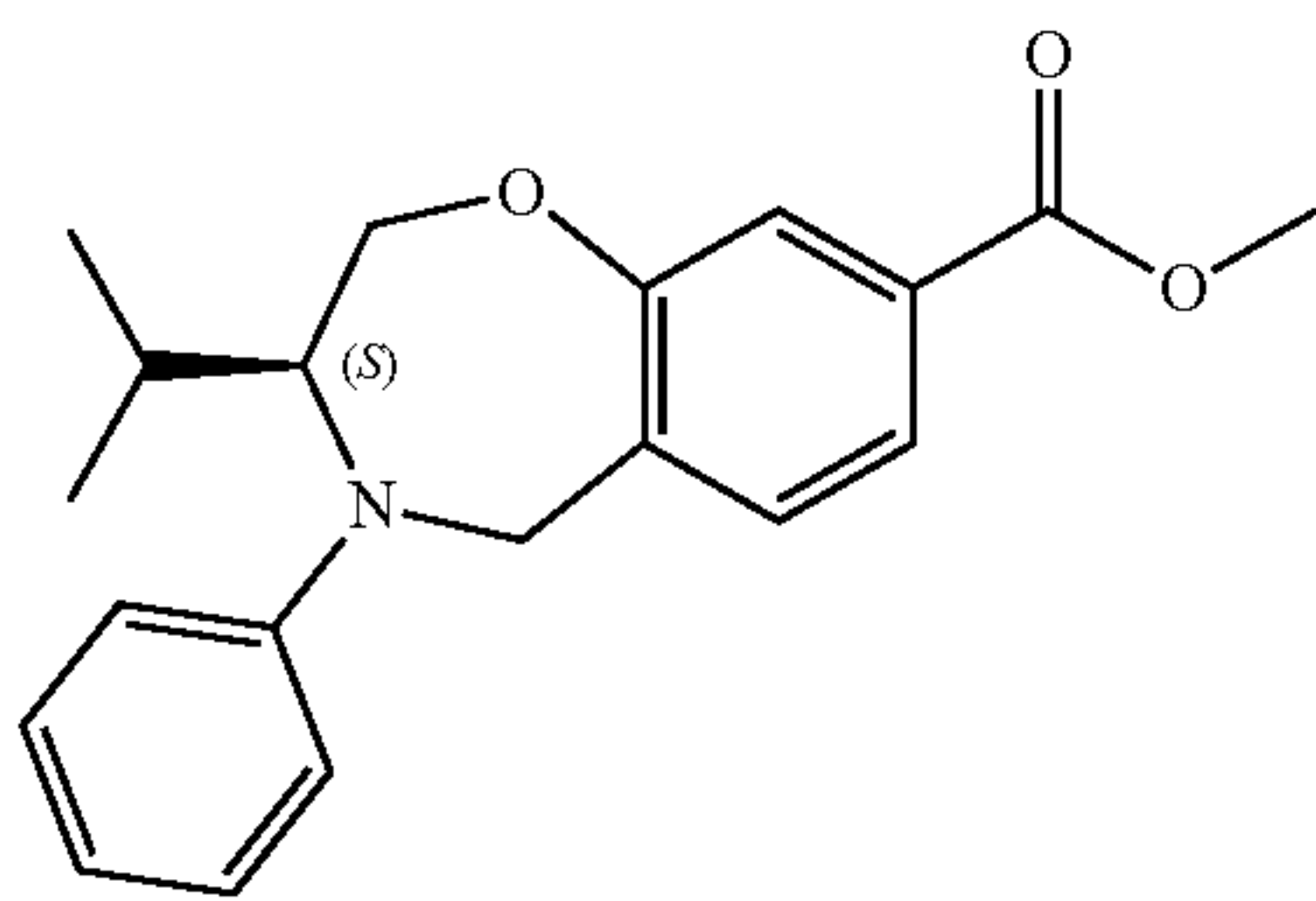
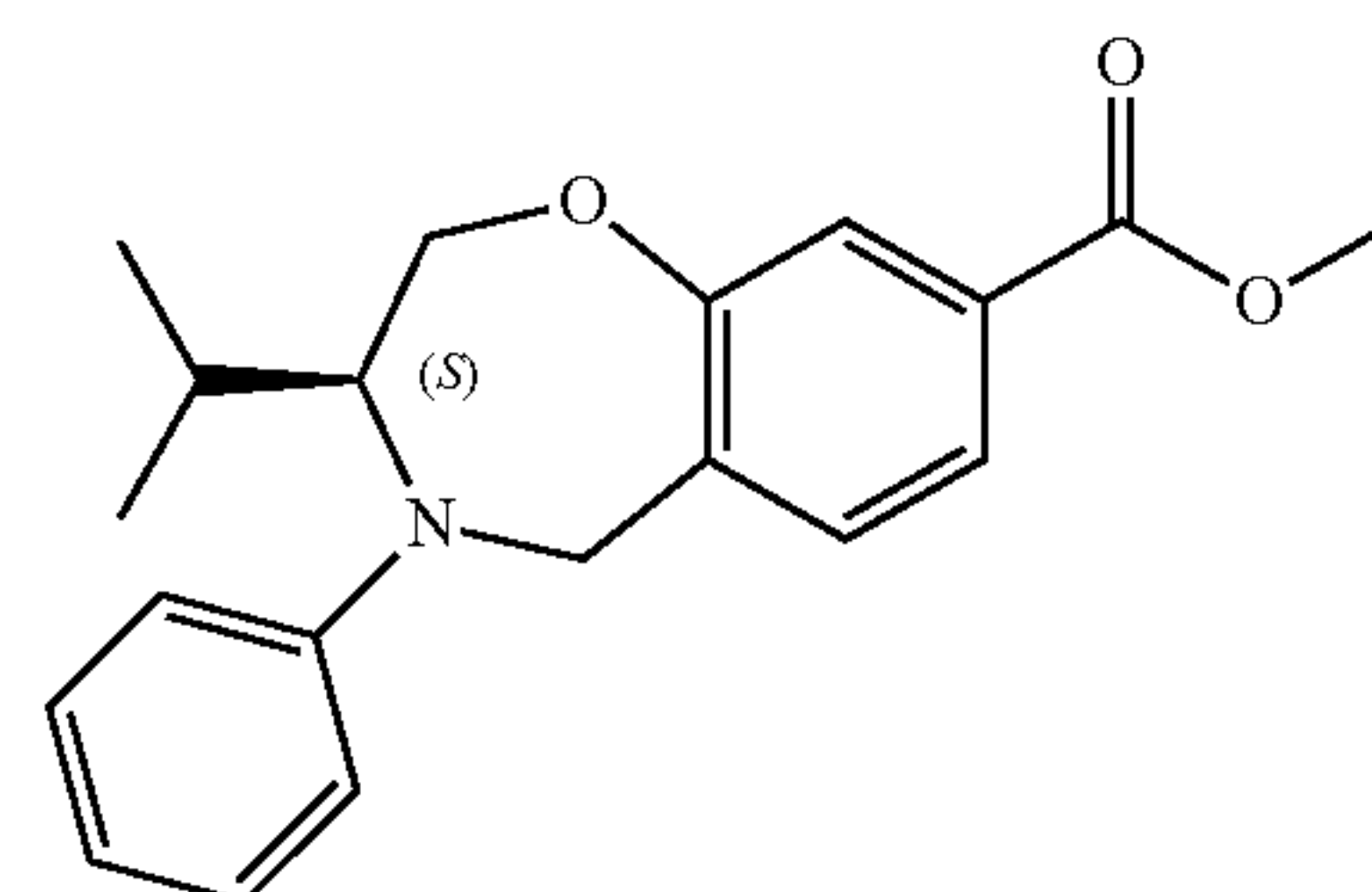
## Example 30

## Step-1: Methyl (S)-3-isopropyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

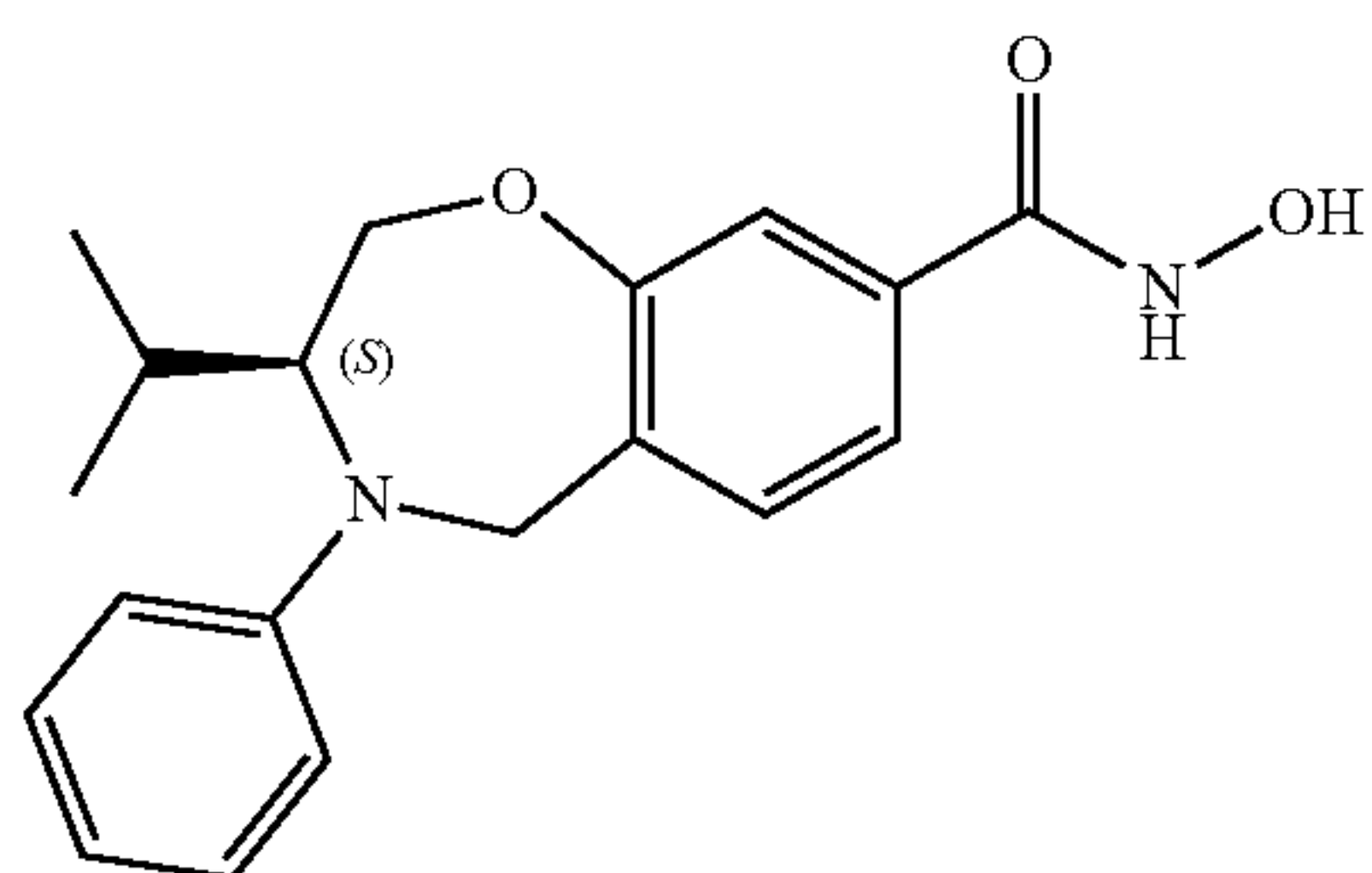
Preparation of (S)—N-hydroxy-3-isopropyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



step 1



step 2



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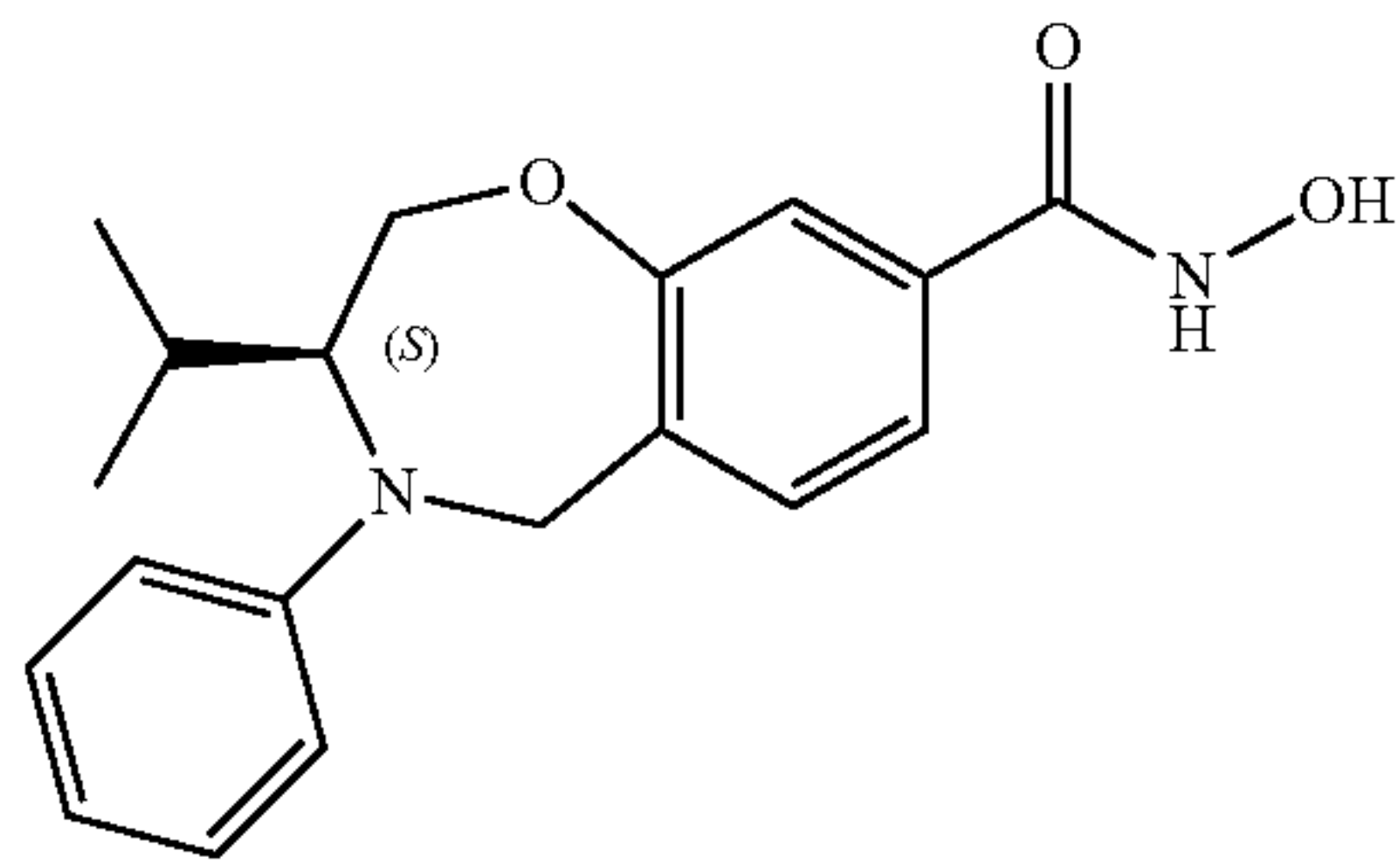
65

Into a 8-mL vial purged and maintained with an inert atmosphere of nitrogen, were placed a solution of methyl (S)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (200 mg, 0.80 mmol, 1 equiv) in toluene (3 mL), iodobenzene (490 mg, 2.40 mmol, 3 equiv), Pd(OAc)<sub>2</sub> (40 mg, 0.18 mmol, 0.2 equiv), BINAP (200 mg, 0.32 mmol, 0.4 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (800 mg, 2.44 mmol, 3 equiv). The resulting mixture was stirred for 16 h at 110° C. in an oil bath and then concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (10 mL). The resulting solution was extracted with EtOAc (3×10 mL), washed with H<sub>2</sub>O (3×10 mL) and then concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:4) to afford the title compound as a brown oil (40 mg, 15% yield). MS: (ES, m/z): 326 [M+H]<sup>+</sup>.



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Step-2: (S)—N-Hydroxy-3-isopropyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed a solution of methyl (S)-3-isopropyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]ox-

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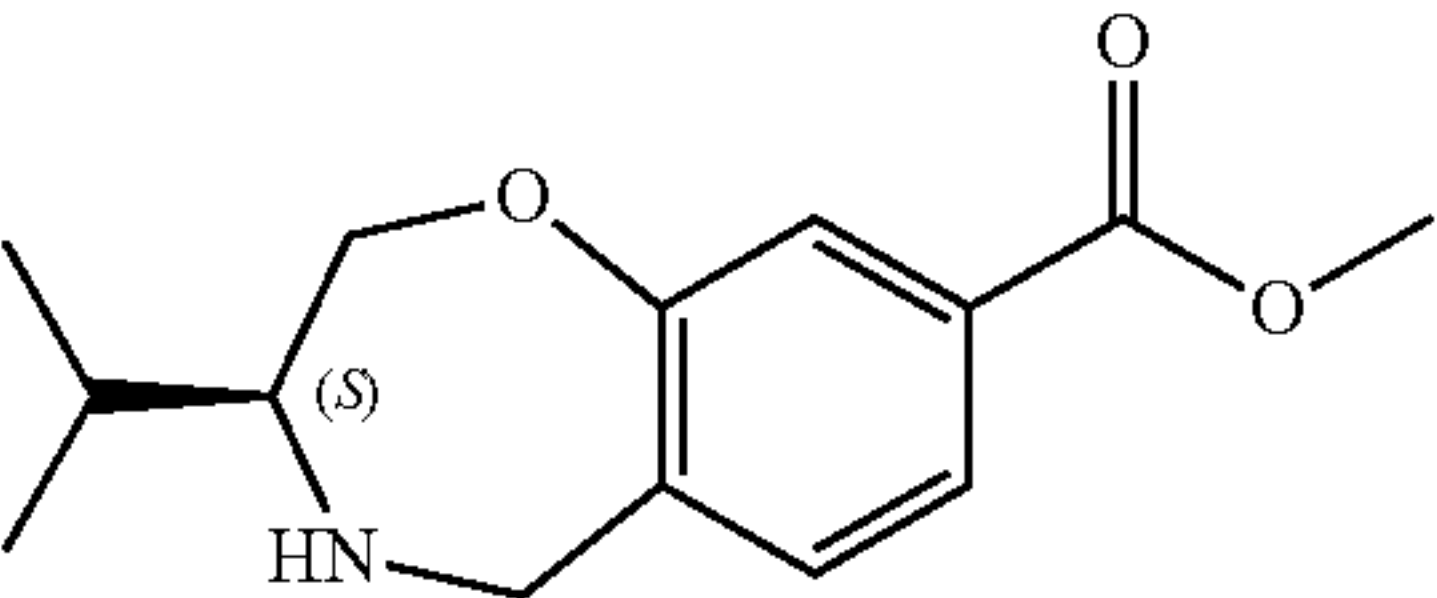
azepine-8-carboxylate (40 mg, 0.12 mmol, 1 equiv) in THF:MeOH (2 mL, 4:1). This was followed by the addition of NH<sub>2</sub>OH (50% in water, 0.25 mL, 30 equiv) and aq. 1N NaOH (0.25 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 5% B to 78% B in 7 min; Detector, UV 254, 220 nm) to afford the title compound as an off-white solid (7.5 mg, 14% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.08 (s, 1H), 8.97 (s, 1H), 7.49-7.47 (d, J=8.0 Hz, 1H), 7.35-7.33 (d, J=8.0 Hz, 1H), 7.08-7.01 (m, 3H), 6.71-6.69 (d, J=8.0 Hz, 2H), 6.53-6.50 (m, 1H), 4.93-4.80 (m, 1H), 4.50-4.23 (m, 3H), 3.98-3.79 (m, 1H), 2.11-1.95 (m, 1H), 1.07-0.96 (m, 6H). MS: (ES, m/z): 327 [M+H]<sup>+</sup>.

TABLE 9

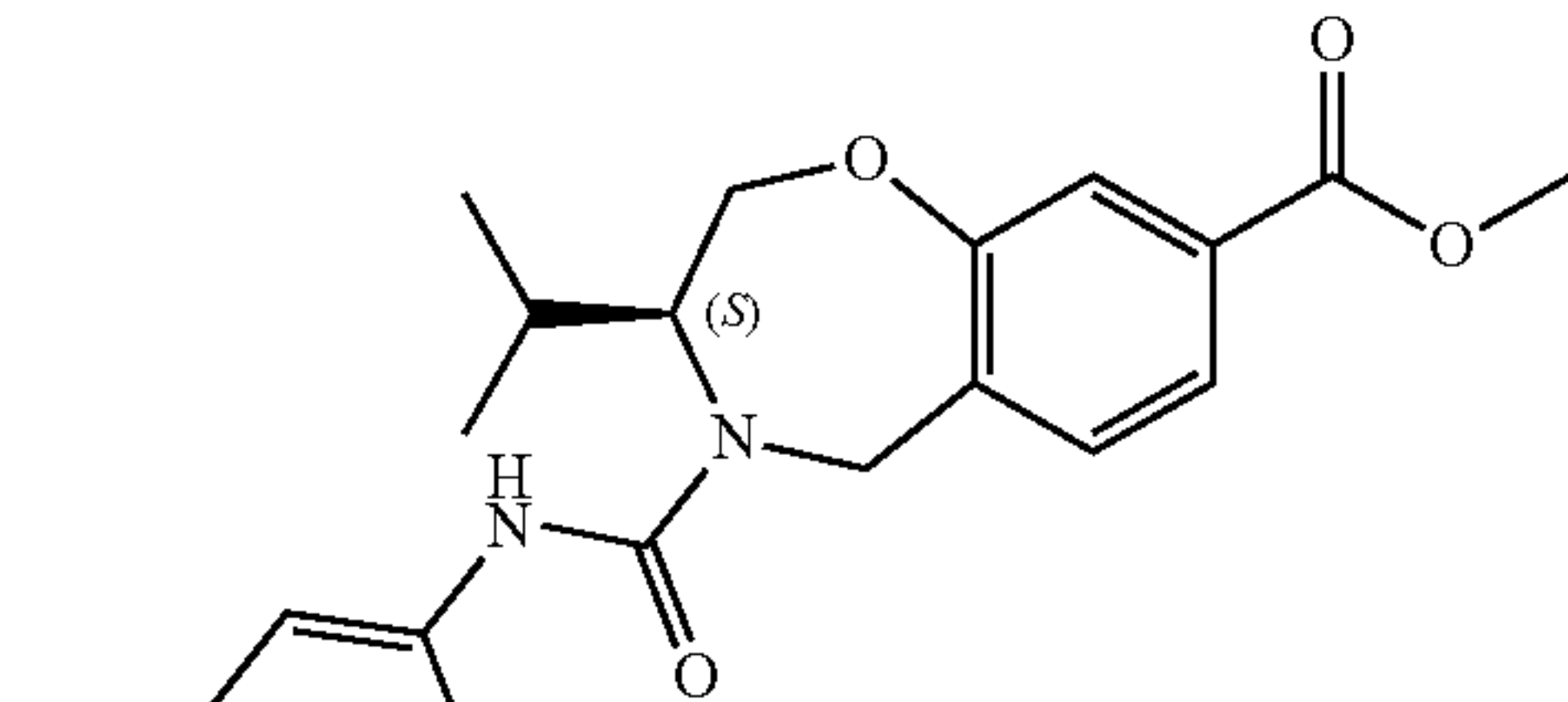
The following compound was prepared according to the method of Example 30, using methyl (R)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 327 [M + H] <sup>+</sup>	11.08-11.05 (s, 1H), 9.03-8.95 (br, 1H), 7.49-7.47 (d, J = 8.0 Hz, 1H), 7.35-7.33 (d, J = 8.0 Hz, 1H), 7.11-6.94 (m, 3H), 6.79-6.63 (m, 2H), 6.52-6.41 (m, 1H), 4.94-4.90 (d, J = 17.6 Hz, 1H), 4.49-4.32 (m, 3H), 3.94-3.84 (m, 1H), 2.08-1.98 (m, 1H), 1.08-0.97 (m, 6H)

Example 31

Preparation of (S)—N8-hydroxy-3-isopropyl-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



step 1

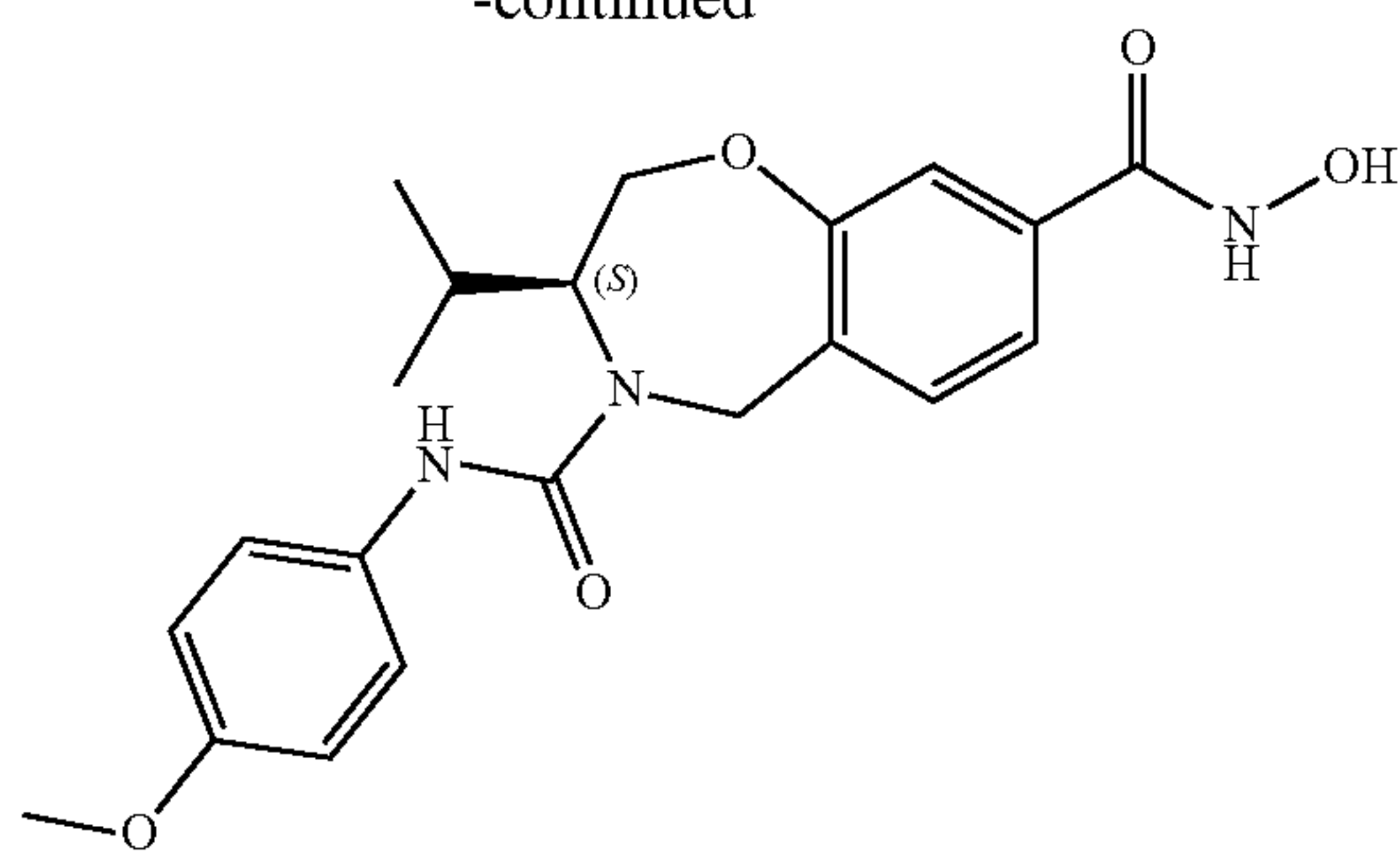


step 2

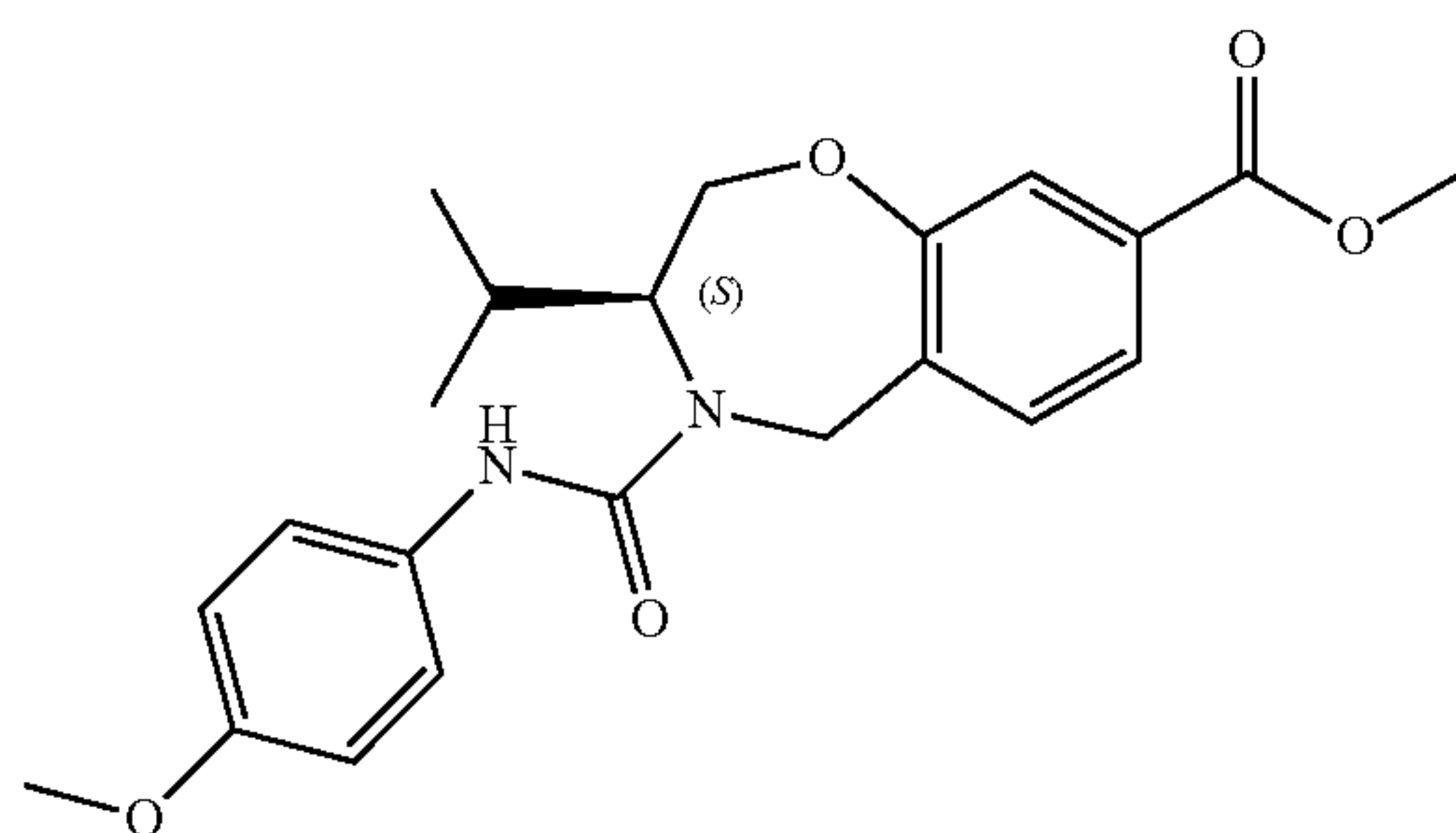


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-continued



Step-1: Methyl (S)-3-isopropyl-4-((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

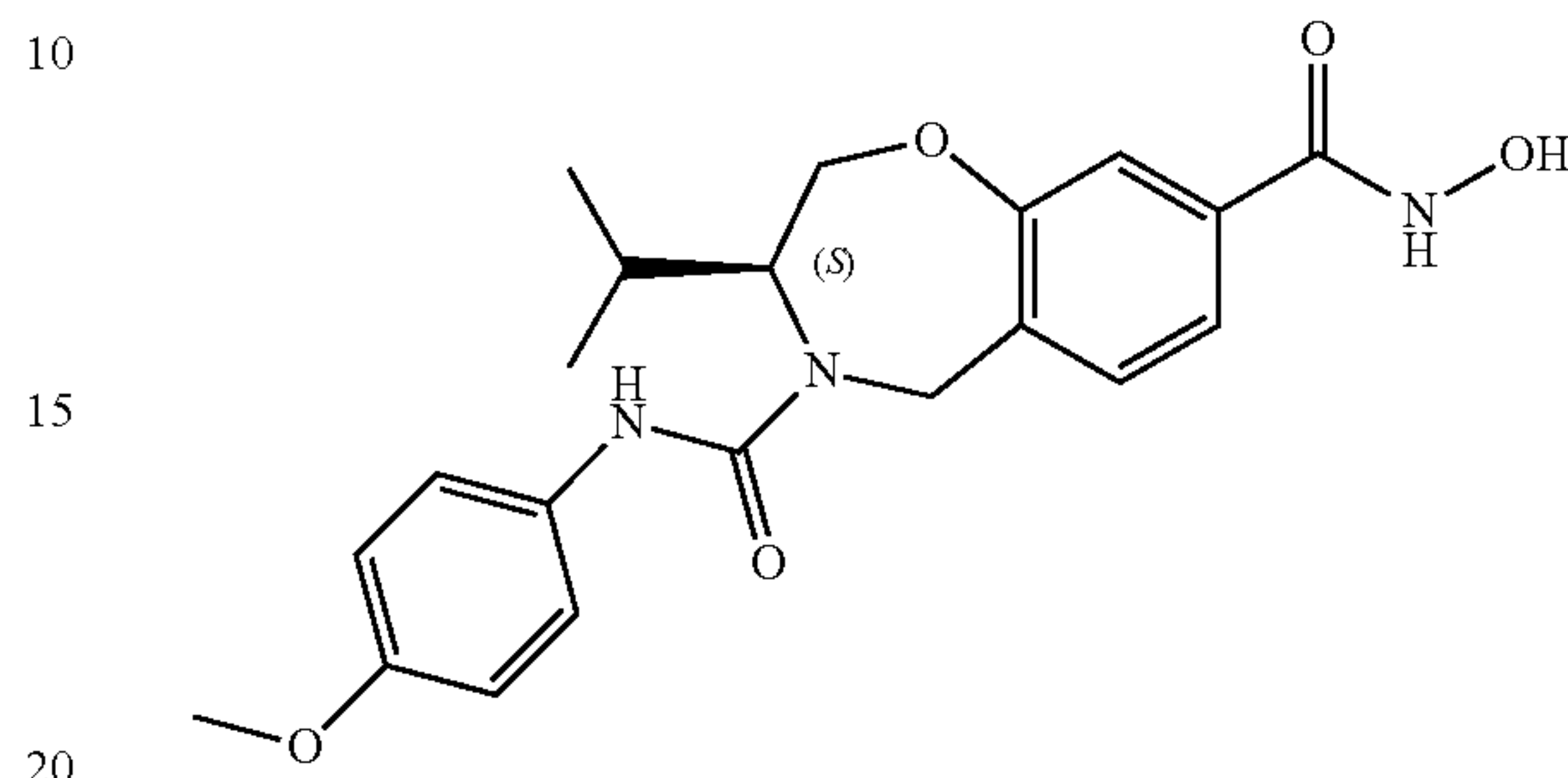


Into a 8-mL vial, were placed a solution of methyl (S)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (150 mg, 0.60 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL), Et<sub>3</sub>N (183 mg, 1.81 mmol, 3 equiv) and 1-isocyanato-4-methoxybenzene (135 mg, 0.91 mmol, 1.5 equiv). The resulting mixture was stirred overnight at room temperature and then concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:2) to afford the title

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compound as a pink solid (250 mg) which was used without further purification. MS: (ES, m/z): 399 [M+H]<sup>+</sup>.

Step-2: (S)—N8-Hydroxy-3-isopropyl-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



Into a 8-mL vial, was placed a solution of methyl (S)-3-isopropyl-4-((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.25 mmol, 1 equiv) in THF:MeOH (2.0 mL, 4:1), then aq. 1N NaOH (0.75 mL, 2 equiv) and NH<sub>2</sub>OH (50% in H<sub>2</sub>O, 0.75 mL, 30 equiv) were added. The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 4% B to 32% B in 7 min; Detector, UV 254, 220 nm) to afford the title compound as a pink solid (75 mg, 75% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.12 (s, 1H), 9 (s, 1H), 8.14 (s, 1H), 7.32-6.76 (m, 7H), 4.91-4.87 (d, 1H), 4.58-4.54 (d, 1H), 4.35-4.26 (m, 3H), 3.69-3.67 (s, 3H), 2-1.97 (s, 1H), 0.99-0.97 (d, 3H, J=8.0 Hz), 0.95-0.93 (d, 3H, J=8.0 Hz). MS: (ES, m/z): 400 [M+H]<sup>+</sup>.

TABLE 10

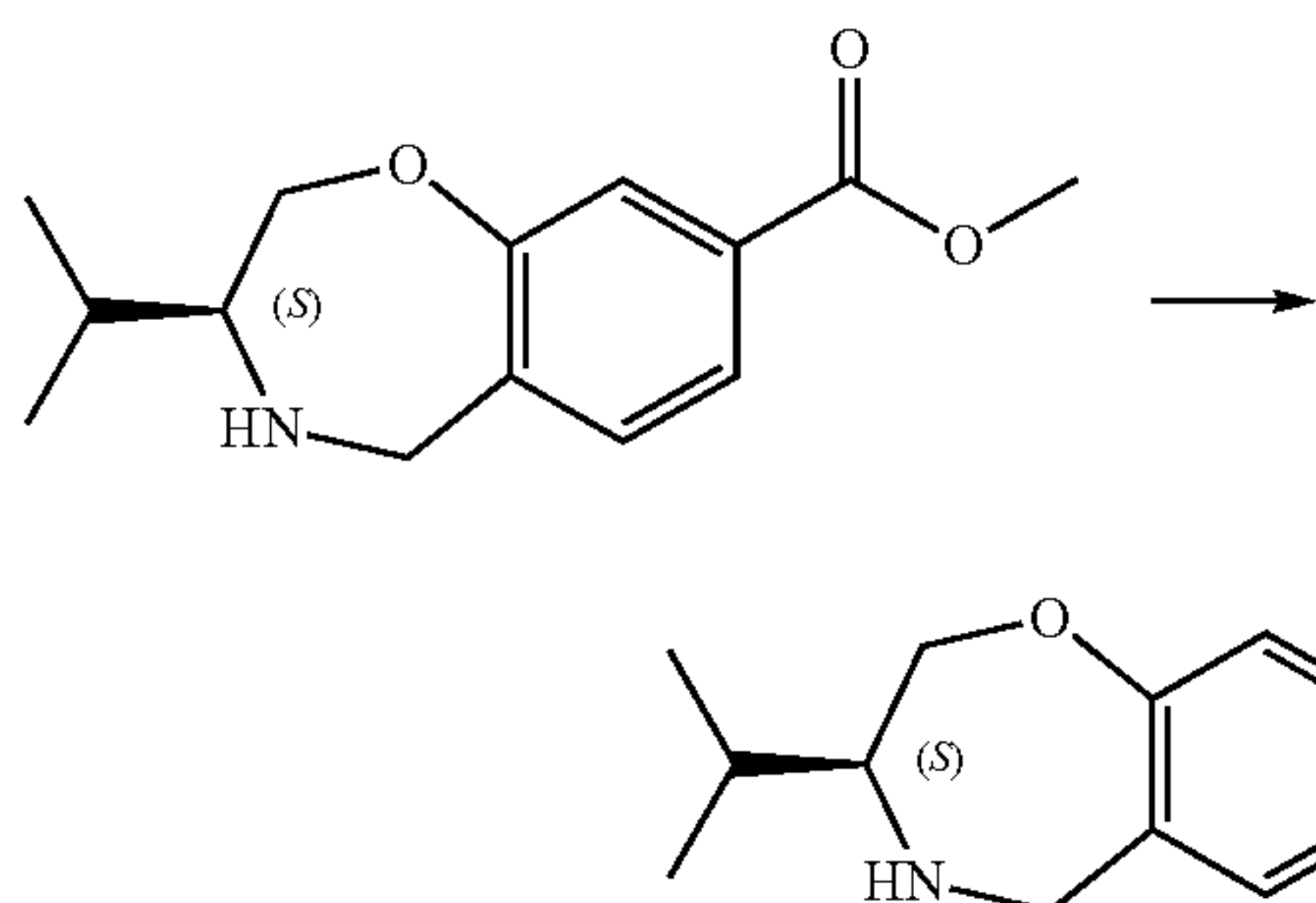
The following compound was prepared according to the method of Example 31, using methyl (R)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate.

Structure	Found	
	M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 400 [M + H] <sup>+</sup>	11.12 (br s, 1H), 8.14 (s, 1H), 7.39-7.30 (s, 2H), 7.29-7.12 (m, 3H), 6.83-6.71 (m, 2H), 4.96-4.82 (d, J = 23.2 Hz, 1H), 4.62-4.48 (d, J = 23.2 Hz, 1H), 4.41-4.21 (m, 3H), 3.67 (s, 3H), 2.09-1.84 (m, 1H), 1.04-0.87 (m, 6H)

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## Example 32

Preparation of (S)—N-hydroxy-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



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Into a 8-mL vial, was placed a solution of methyl (S)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.40 mmol, 1 equiv) in THF:MeOH (2 mL, 4:1). This was followed by the addition of  $\text{NH}_2\text{OH}$  (50% in  $\text{H}_2\text{O}$ , 398 mg, 12.05 mmol, 30 equiv) and aq. 1N NaOH (32 mg, 0.80 mmol, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge RP C18 OBD, 5  $\mu\text{m}$ , 19 $\times$ 50 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN/0.05% formic acid; Flow rate: 23 mL/min; Gradient: 2% B to 10% B in 7 min; Detector, UV 254, 220 nm) to afford the title compound as a pink solid (99 mg, 68% yield).  $^1\text{H}$ -NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.30 (s, 1H), 9.31 (s, 1H), 7.53-7.40 (m, 3H), 4.55-4.34 (m, 3H), 4-3.95 (m, 1H), 3.51 (s, 1H), 2.10-2.06 (m, 1H), 1.03-1.02 (d,  $J=4.0$  Hz, 3H), 0.98-0.96 (d,  $J=8.0$  Hz, 3H). MS: (ES,  $m/z$ ): 250  $[\text{M}+\text{H}]^+$ .

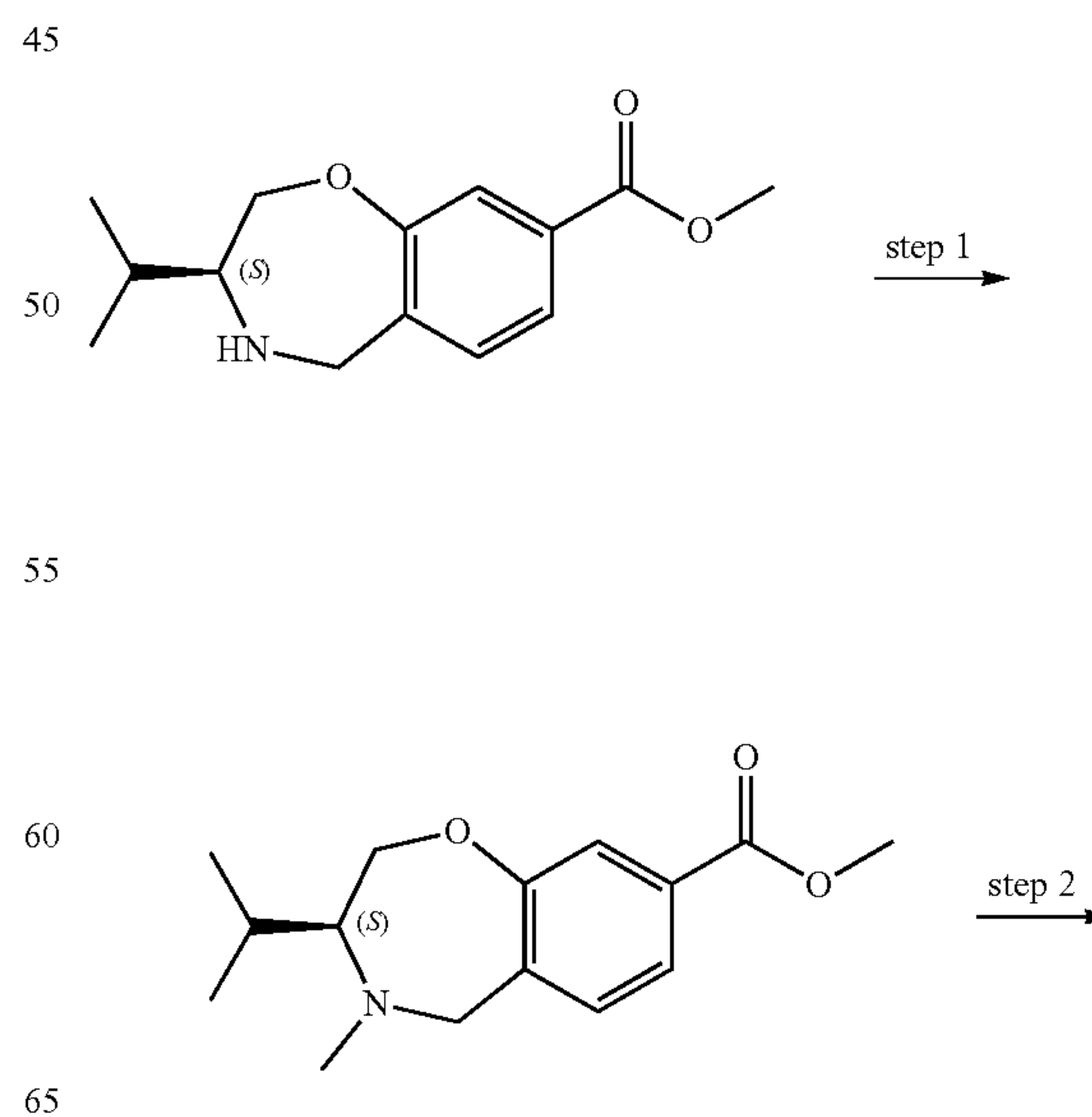
TABLE 11

The following compound was prepared according to the method of Example 32, using methyl (R)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate.

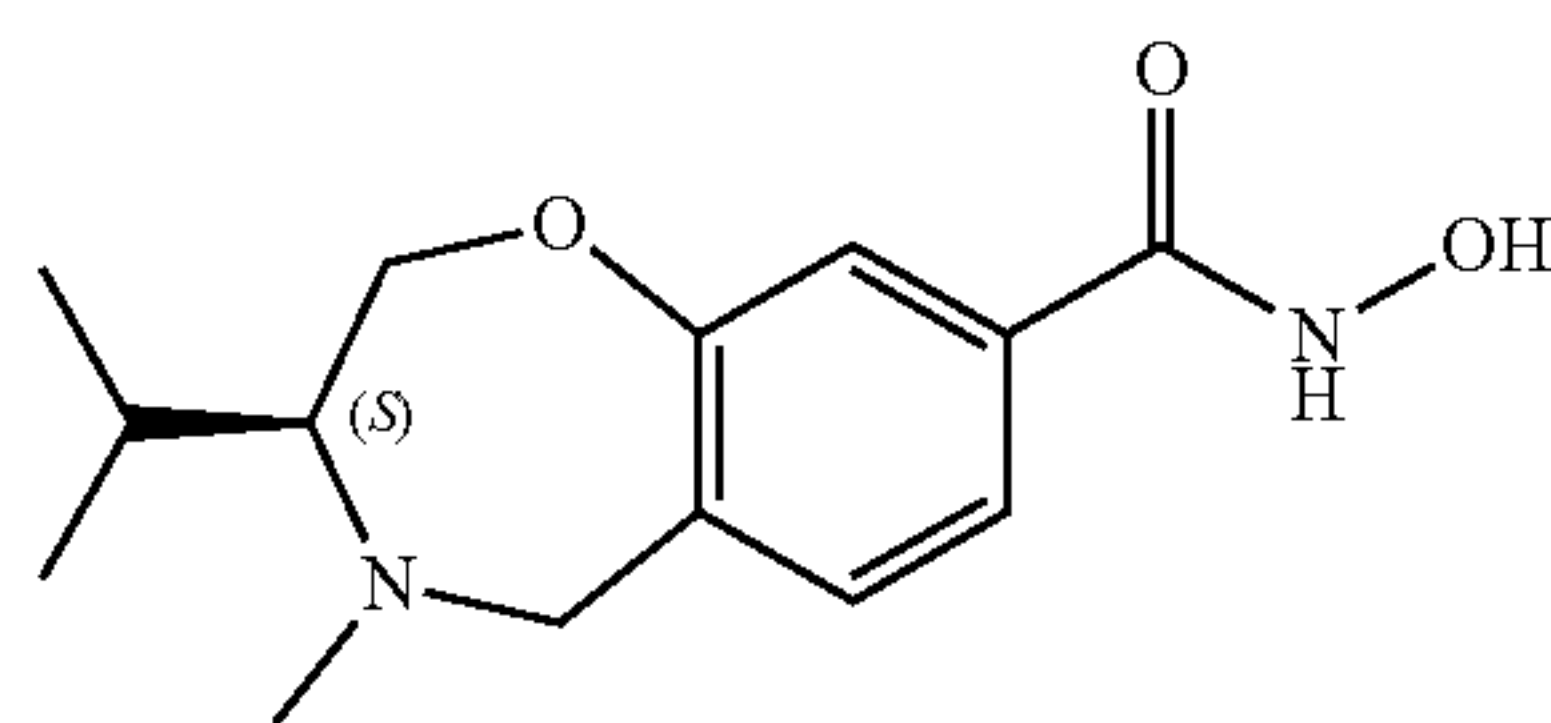
Structure	Found M + H	$^1\text{H}$ -NMR (400 MHz, $\text{DMSO-d}_6$ ) $\delta$ (ppm)
	(ES, $m/z$ ): 250 [M + H] $^+$	11.31 (br s, 1H), 9.42-9.31 (br s, 1H), 9.11-9.04 (m, 2H), 7.54-7.49 (m, 2H), 7.41 (s, 1H), 4.56-4.35 (m, 3H), 4.01-3.96 (m, 1H), 3.52 (s, 1H), 2.13-2.05 (m, 1H), 1.04-0.97 (m, 6H)

## Example 33

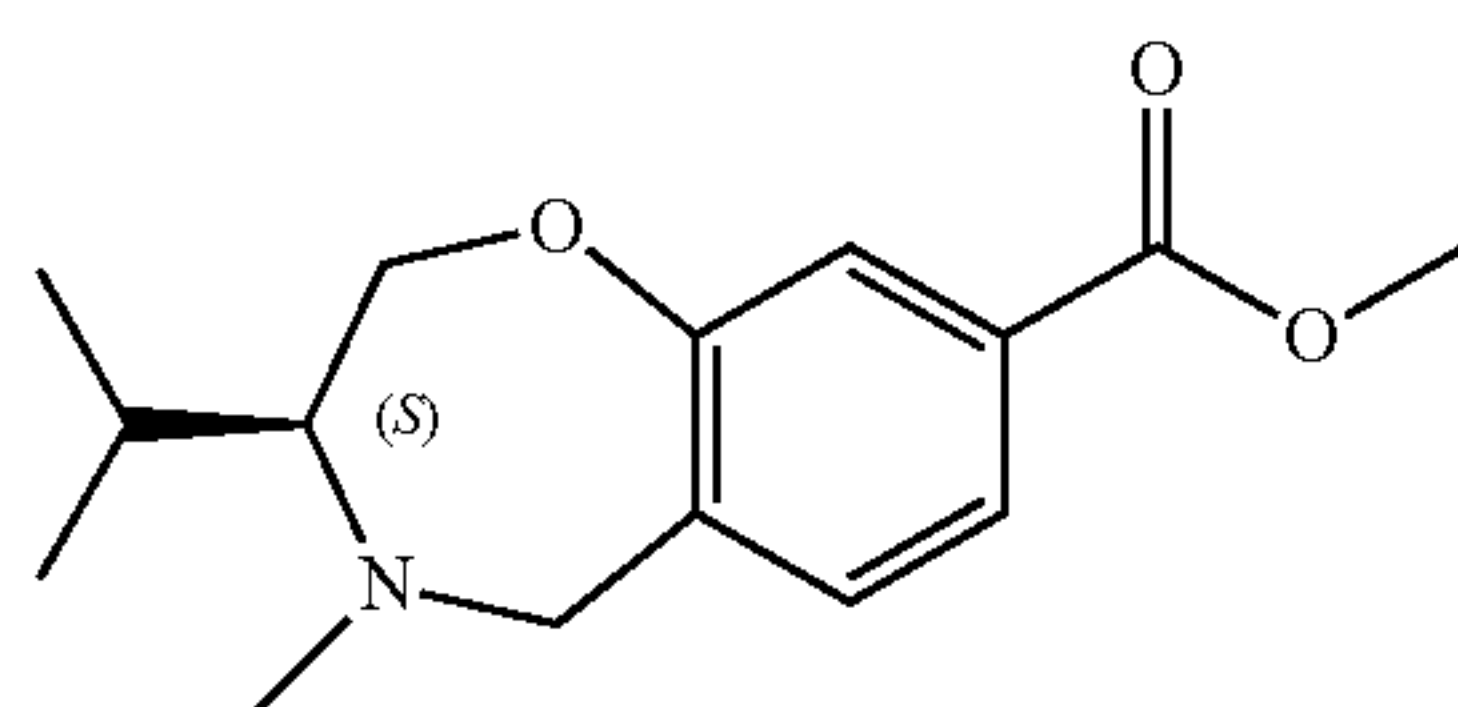
Preparation of (S)—N-hydroxy-3-isopropyl-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide





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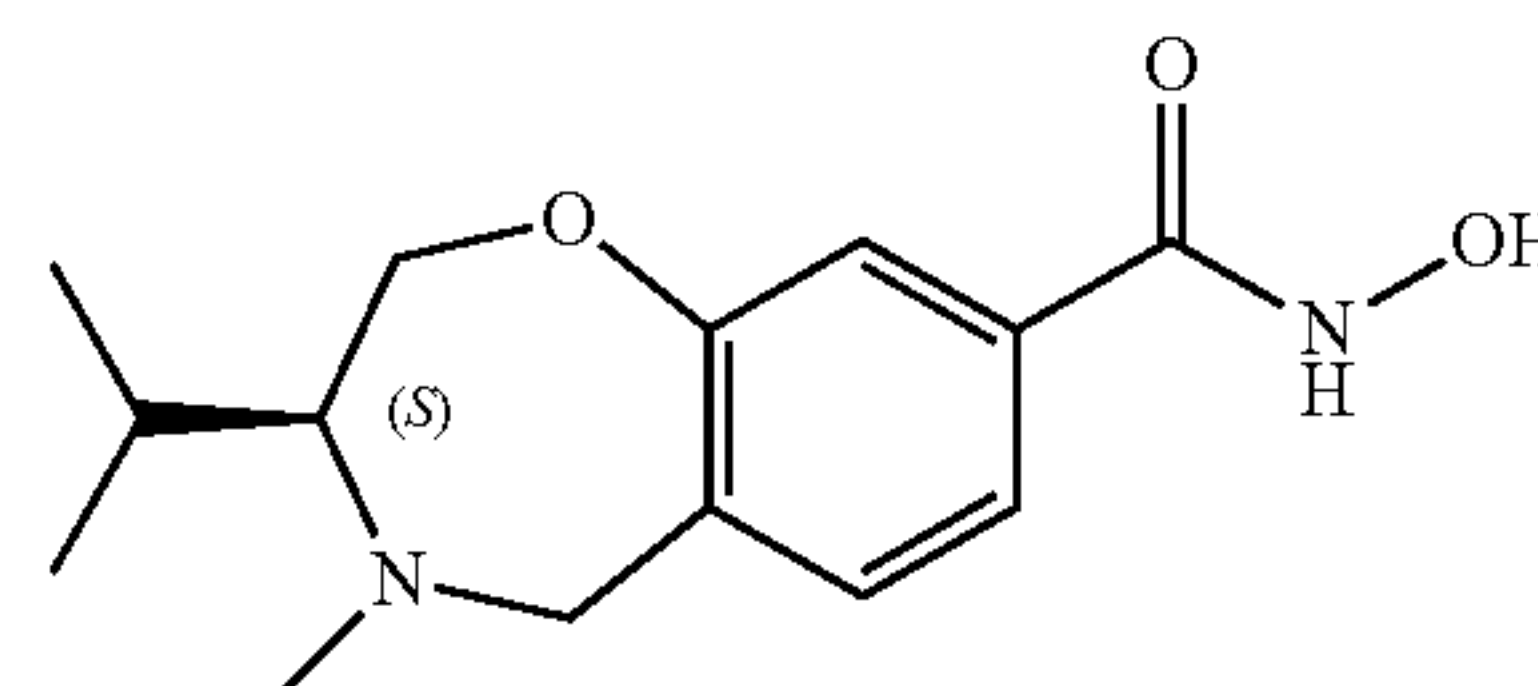
Step-1: Methyl (S)-3-isopropyl-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, were placed a solution of methyl (S)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (150 mg, 0.60 mmol, 1 equiv) in acetic acid (3.0 mL) and paraformaldehyde (180 mg, 5.62 mmol, 10 equiv). The resulting solution was stirred for 2 h at room temperature. Then NaBH(OAc)<sub>3</sub> (2.54 g, 20 equiv) was added at 0° C. The reaction was stirred for an additional 1 day at room temperature and then concentrated under vacuum to afford the title compound as light yellow oil (190 mg) which was used without purification. MS: (ES, m/z): 264 [M+H]<sup>+</sup>.

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Step-2: (S)—N-Hydroxy-3-isopropyl-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed a solution of methyl (S)-3-isopropyl-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (90 mg, 0.34 mmol, 1 equiv) in THF:MeOH (2 mL, 4:1), followed by the addition of NH<sub>2</sub>OH (50% in water, 0.67 mL, 10.27 mmol, 30 equiv) and aq. 1N NaOH (0.68 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 3% B to 10% B in 7 min; Detector, UV 254, 220 nm) to afford the title compound as an orange semi-solid (35 mg, 27% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.31 (s, 1H), 10.25-9.78 (s, 1H), 9.14-9.05 (s, 1H), 7.56-7.33 (m, 3H), 4.91-4.73 (s, 0.5H), 4.68-4.60 (d, 2.5H), 4.60-4.33 (m, 0.4H), 4.30-4.16 (m, 0.6H), 3.99-3.22 (m, 2H), 3.67-2.64 (s, 2H), 2.51-2.33 (m, 0.7H), 2.11-1.88 (m, 0.3H), 1.10-0.89 (m, 6H). MS: (ES, m/z): 265 [M+H]<sup>+</sup>.

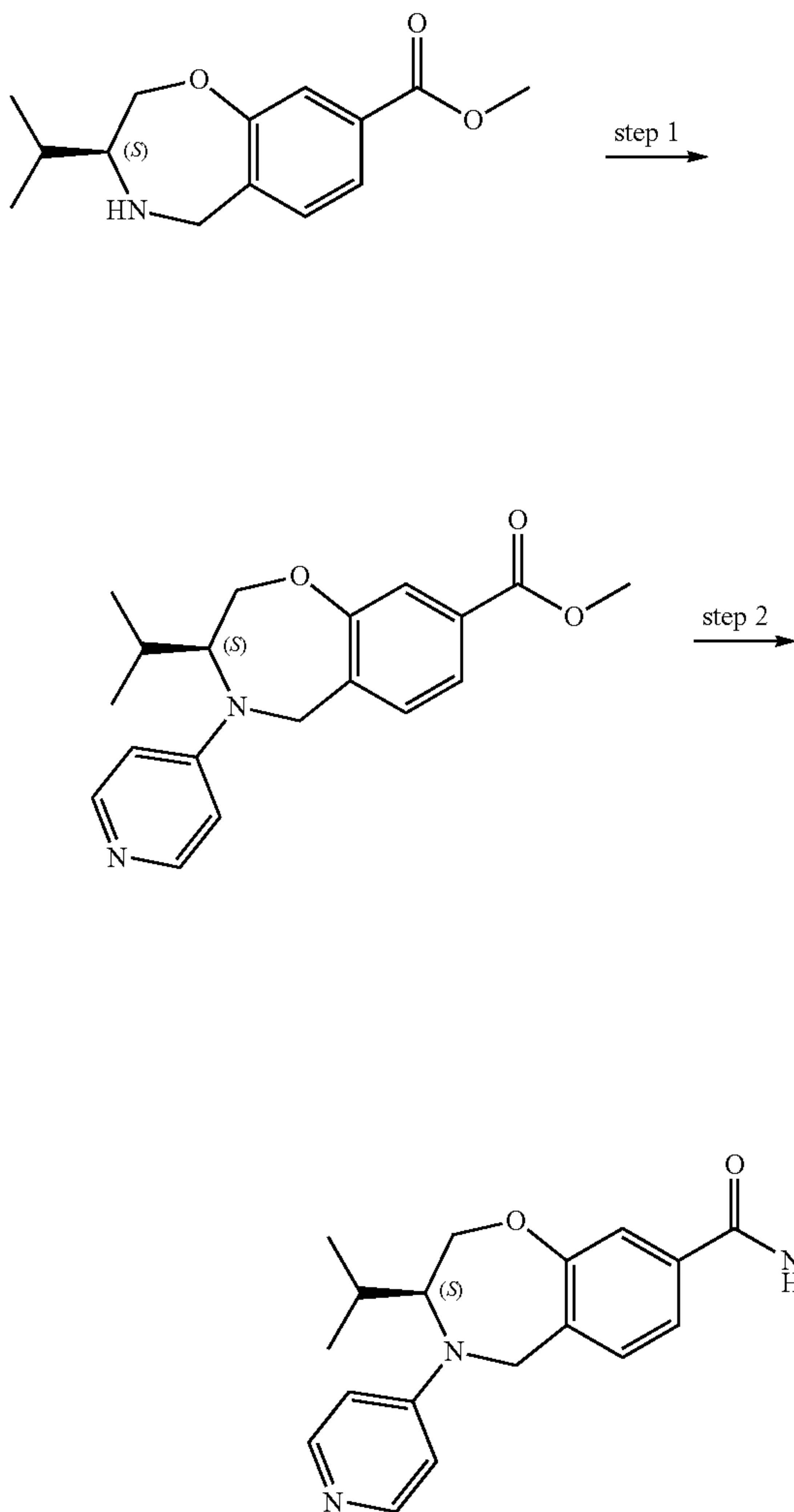
TABLE 12

The following compound was prepared according to the method of Example 33, using methyl (R)-3-isopropyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 265 [M + H] <sup>+</sup>	11.30 (br s, 1H), 9.13 (br s, 1H), 7.58-7.27 (m, 3H), 4.84-4.80 (d, J = 12.0 Hz, 1H), 4.49-4.32 (m, 3H), 4.13-3.81 (m, 1H), 2.99-2.88 (s, 2H), 2.61-2.54 (s, 1H), 2.36 (s, 1H), 1.10-1.09 (d, J = 3.0 Hz, 6H)

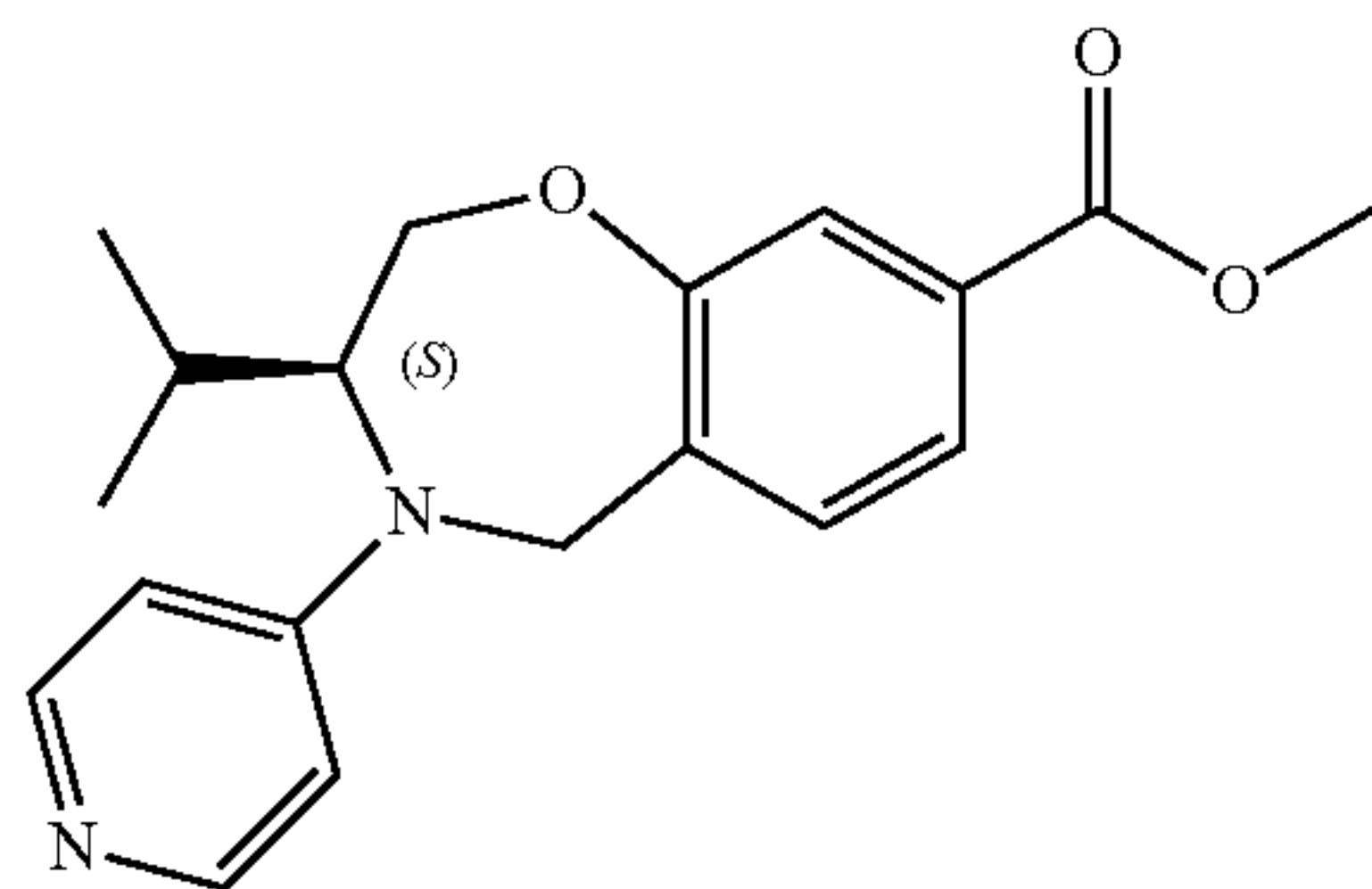
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## Example 34

Preparation of (S)—N-hydroxy-3-isopropyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo [f][1,4]oxazepine-8-carboxamide



Step-1: Methyl (S)-3-isopropyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo [f][1,4]oxazepine-8-carboxylate

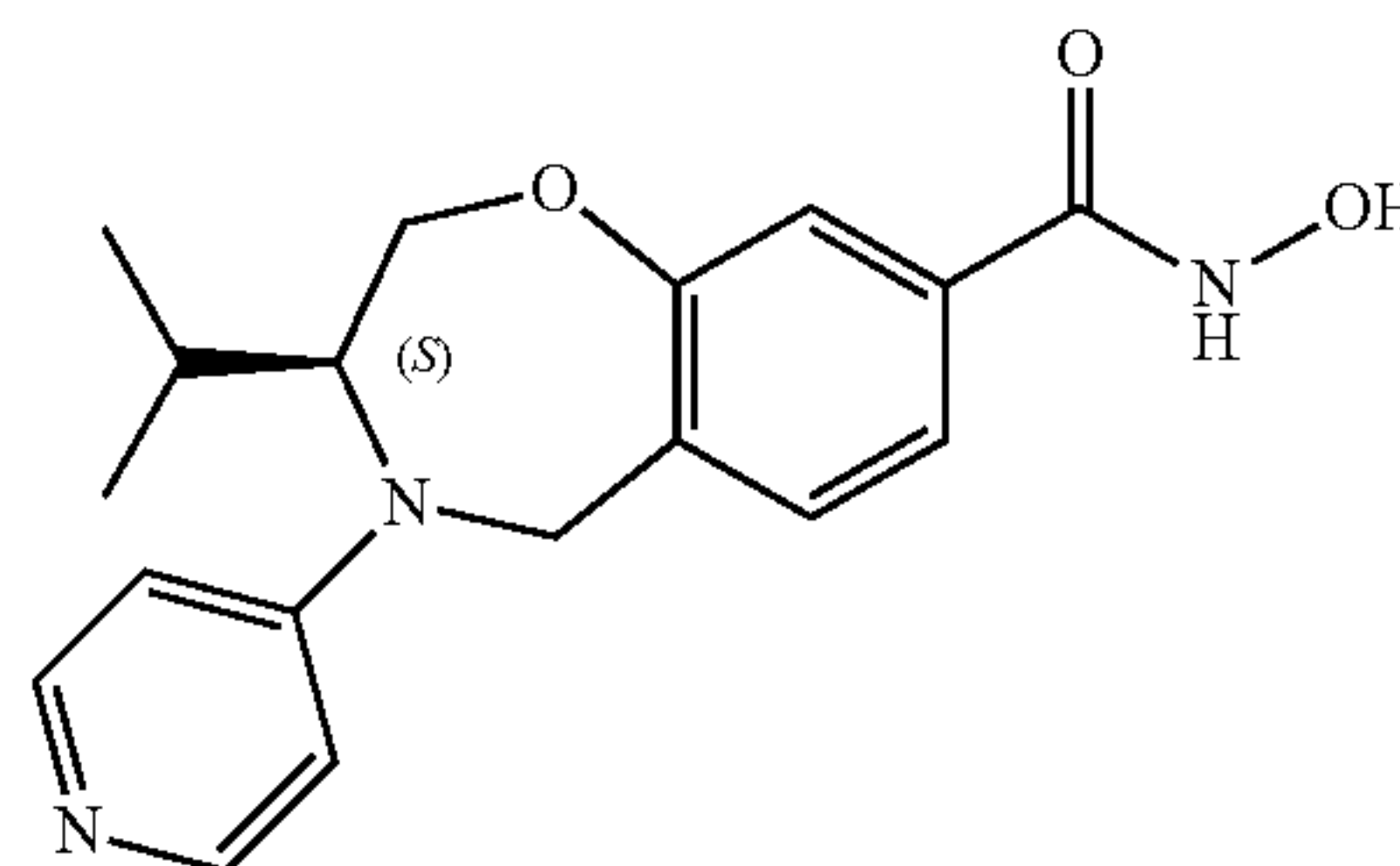


Into a 40-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl (S)-3-isopropyl-2,3,4,5-tetrahydrobenzo [f][1,4]ox-

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azepine-8-carboxylate (250 mg, 1.00 mmol, 1 equiv) in toluene (15 mL), 4-bromopyridine (1.56 g, 8.00 mmol, 8 equiv), RuPhos (187 mg, 0.40 mmol, 0.4 equiv), Pd<sub>2</sub>(dba)<sub>3</sub> (189 mg, 0.18 mmol, 0.2 equiv) and sodium tert-butoxide (480 mg, 5.00 mmol, 5 equiv). The resulting solution was stirred for 20 h at 110° C. in an oil bath. The resulting solution was diluted with H<sub>2</sub>O (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with H<sub>2</sub>O (3×10 mL) and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a brown oil (15 mg, 5% yield). MS: (ES, m/z): 327[M+H]<sup>+</sup>.

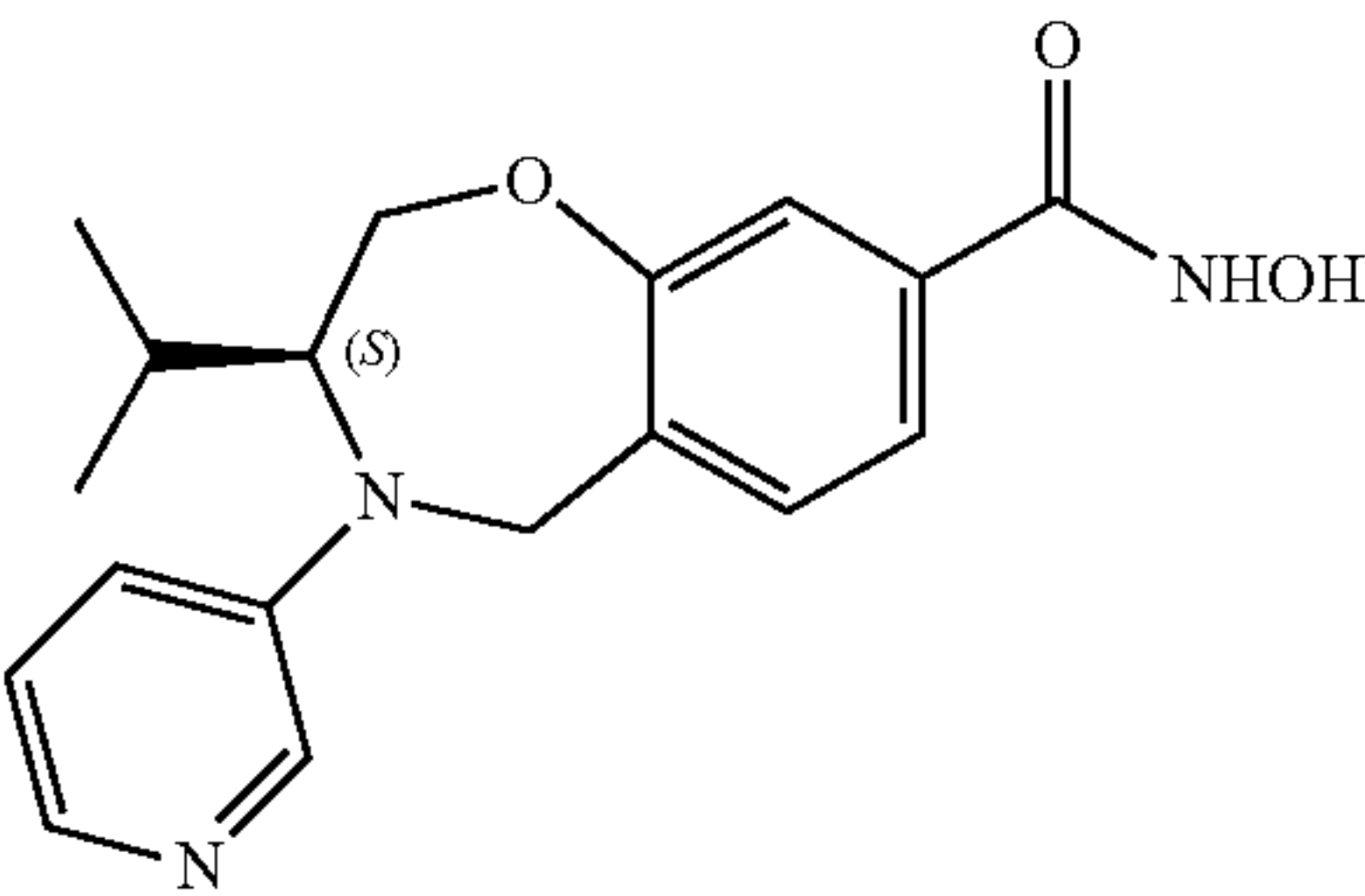
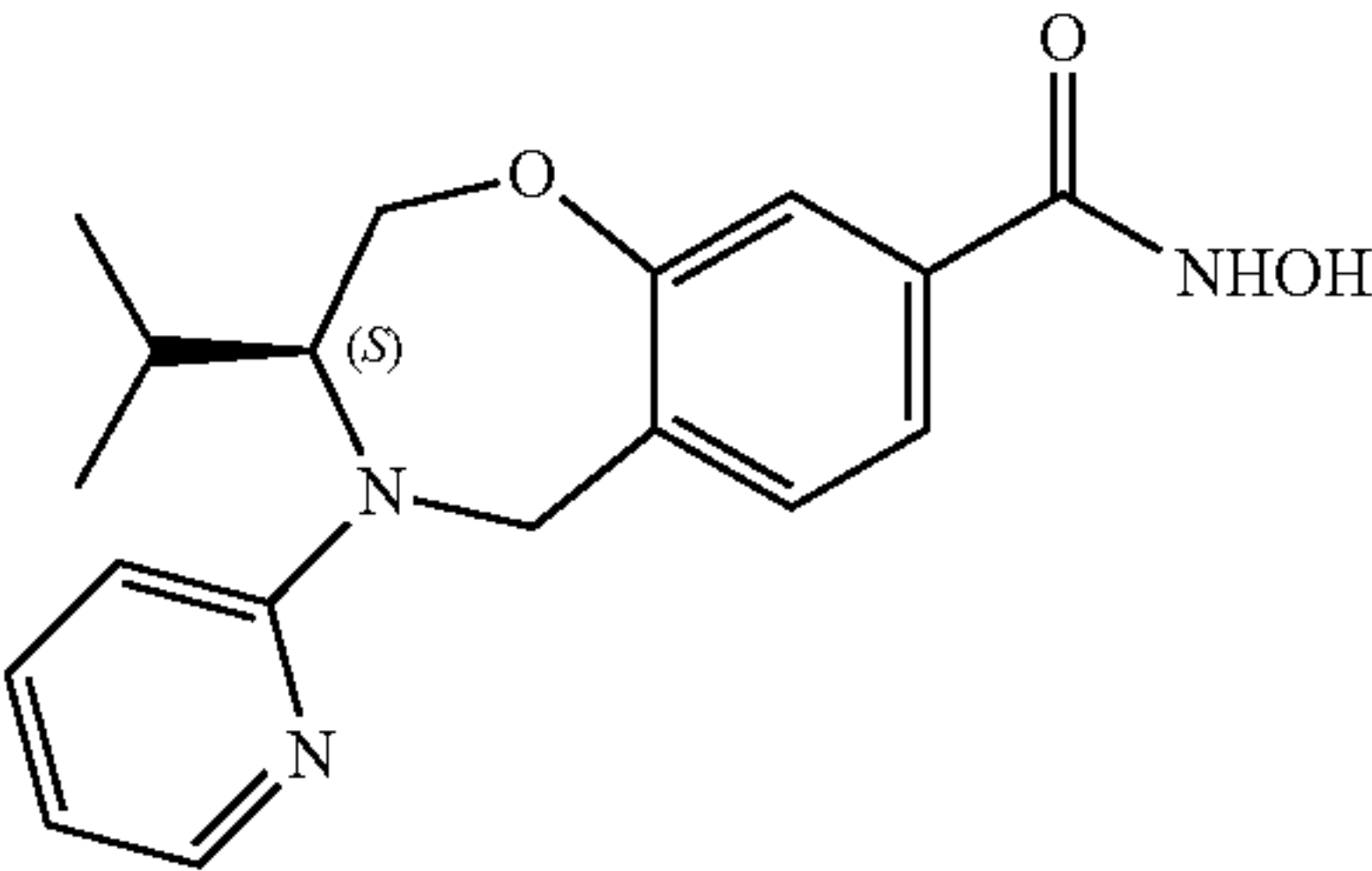
Step-2: (S)—N-Hydroxy-3-isopropyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo [f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed a solution of methyl (S)-3-isopropyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo [f][1,4]oxazepine-8-carboxylate (15 mg, 0.05 mmol, 1 equiv) in THF/MeOH (4:1, 1.5 mL). This was followed by the addition of NH<sub>2</sub>OH (50% in water, 0.1 mL, 30 equiv). To this was added aq. 1N NaOH (0.1 mL, 2 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 5% B to 45% B in 8 min; Detector: UV 254, 220 nm) to afford the title compound as a brown oil (2 mg, 12% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.18 (br s, 1H), 9.05 (br s, 1H), 8.25-8.16 (m, 2H), 7.65-7.63 (m, 1H), 7.51-7.40 (m, 2H), 7.32 (s, 1H), 7.29-7.17 (m, 2H), 7.07-7.04 (m, 1H), 6.93-6.91 (m, 1H), 5.23-5.18 (m, 1H), 4.92-4.79 (m, 1H), 4.58-4.44 (m, 3H), 2.15-2.12 (m, 1H), 1.06-1.04 (d, J=3.2 Hz, 3H), 0.94-0.92 (d, J=3.2 Hz, 3H). MS: (ES, m/z): 328[M+H]<sup>+</sup>.

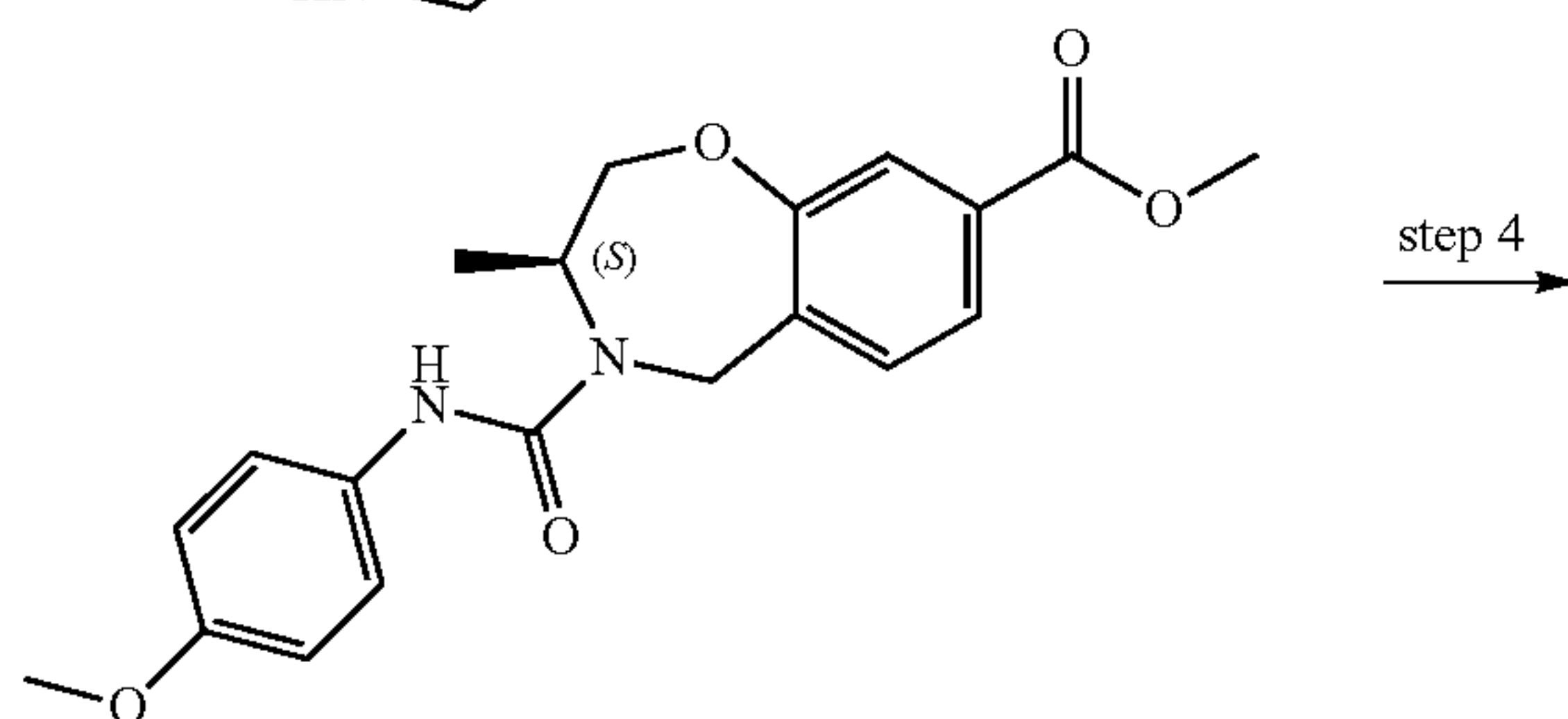
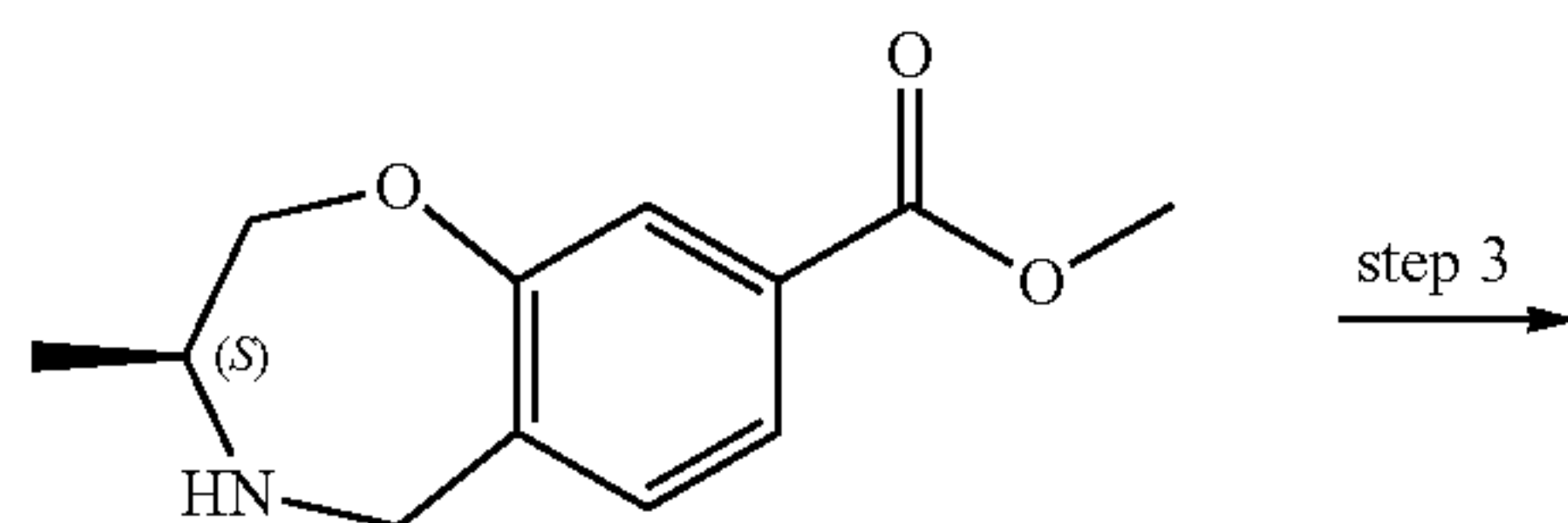
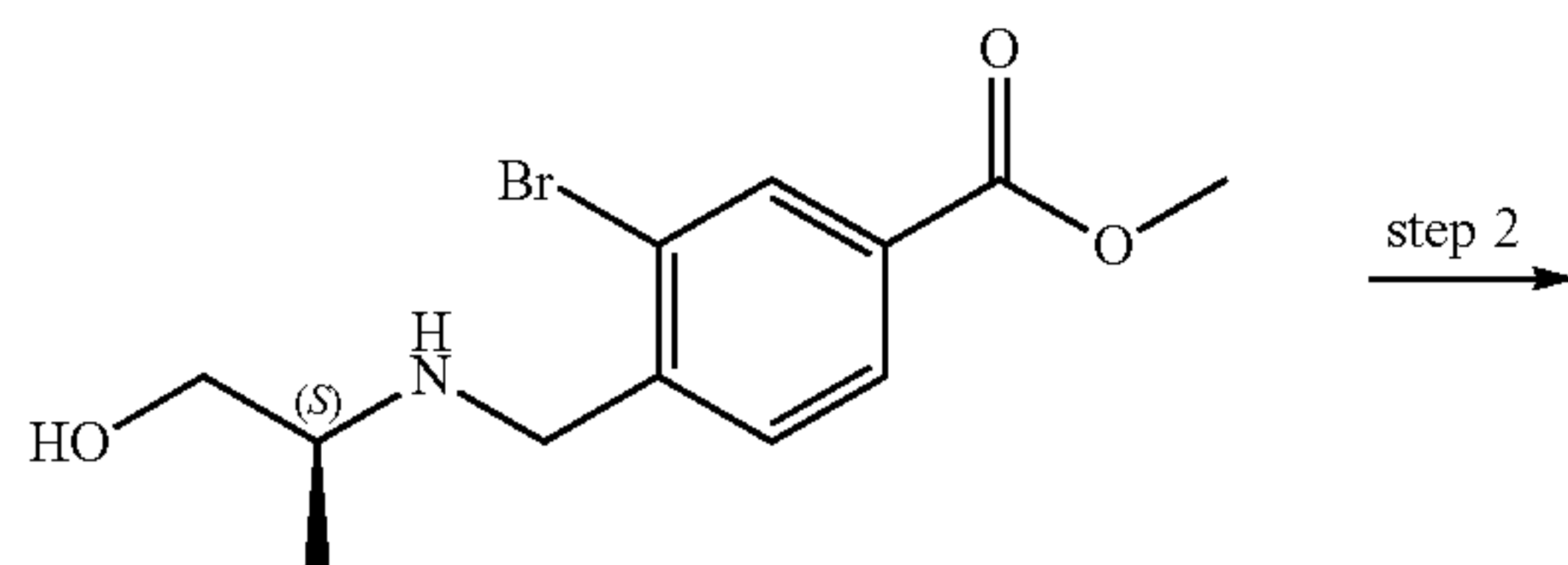
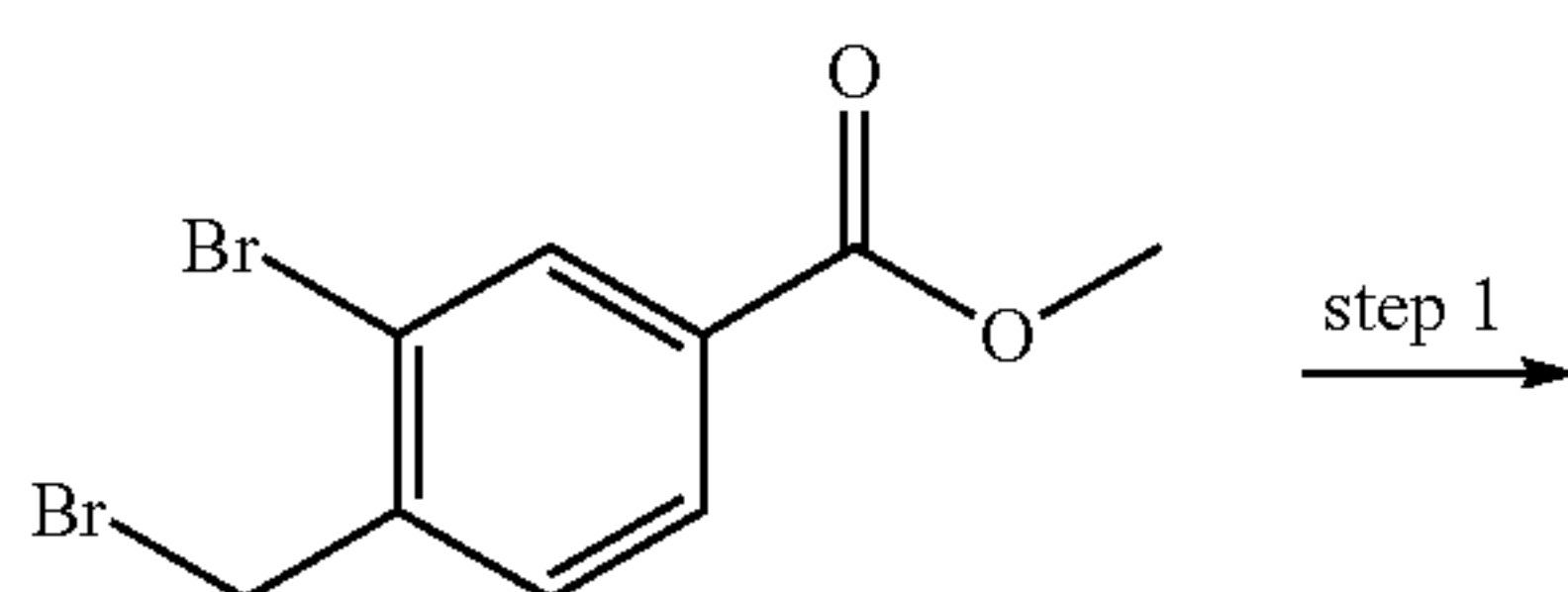


TABLE 13

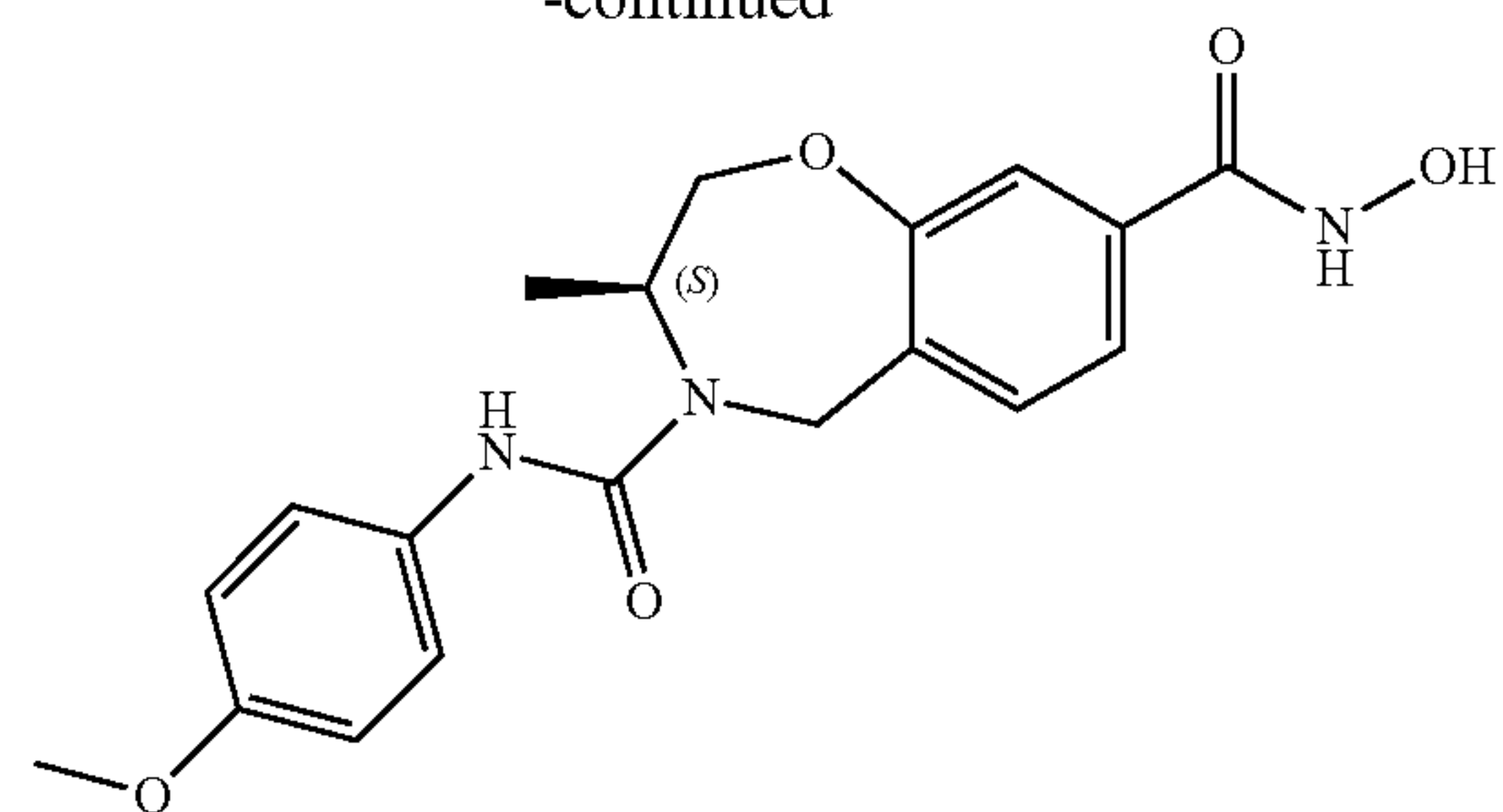
The following compounds were prepared according to the method of Example 34.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 328 [M + H] <sup>+</sup>	11.28 (br s, 1H), 8.29 (s, 1H), 8.04-8.02 (d, J = 2.6 Hz, 1H), 7.96-7.94 (d, J = 3.6 Hz, 1H), 7.74-7.71 (m, 1H), 7.62-7.56 (m, 1H), 7.42-7.40 (m, 1H), 7.18-7.14 (m, 1H), 5.13-5.08 (m, 1H), 4.72-4.68 (m, 1H), 4.51-4.1 (m, 2H), 4.32-4.19 (m, 1H), 2.12-2.07 (m, 1H), 0.98-0.96 (d, J = 3.2 hz, 3H), 0.89-0.87 (d, J = 3.6 Hz, 3H)
	(ES, m/z): 328 [M + H] <sup>+</sup>	11.17 (br s, 1H), 8.02-8.01 (br s, 1H), 7.96-7.84 (m, 1H), 7.71-7.68 (m, 1H), 7.60-7.58 (d, J = 3.6 Hz, 1H), 7.16 (s, 2H), 6.96-6.85 (m, 1H), 5.21-4.97 (m, 2H), 4.84-4.72 (m, 1H), 4.63-4.48 (m, 2H), 2.15-2.13 (m, 1H), 1.07-1.05 (d, J = 3.2 hz, 3H), 0.97-0.96 (d, J = 3.2 hz, 3H)

## Example 35

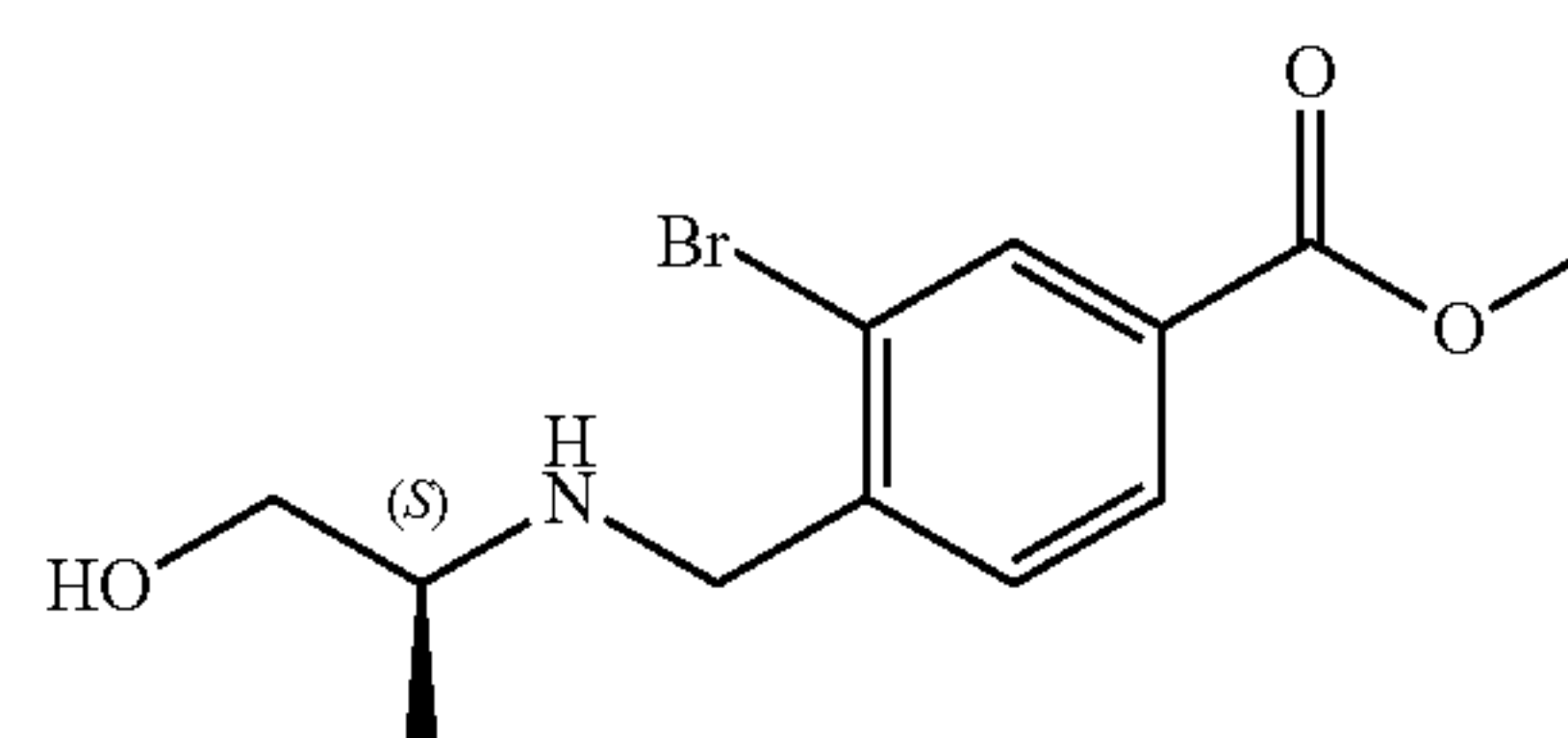
Preparation of (S)—N8-hydroxy-N4-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



-continued



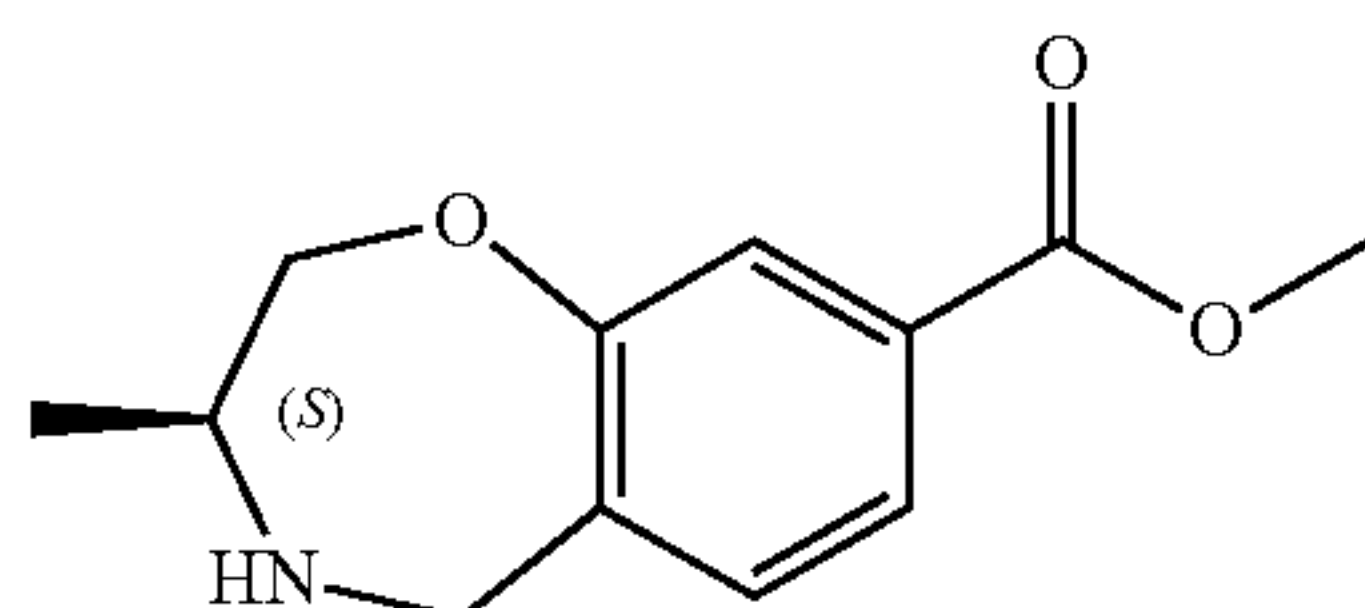
Step-1: Methyl (S)-3-bromo-4-(((1-hydroxypropan-2-yl)amino)methyl)benzoate



Into a 500-mL round-bottom flask, was placed a solution of methyl 3-bromo-4-(bromomethyl)benzoate (10 g, 32.47 mmol, 1 equiv) in THF (150 mL), (S)-2-aminopropan-1-ol (2.4 g, 31.95 mmol, 1 equiv) and K<sub>2</sub>CO<sub>3</sub> (6.7 g, 1.5 equiv). The resulting solution was stirred for 3 h at room temperature, then concentrated under vacuum. The residue was washed with EtOAc/pet. ether (1:10, 20 mL) to afford the title compound as an off-white solid (5 g, 51% yield). MS: (ES, m/z): 302 [M+H]<sup>+</sup>.

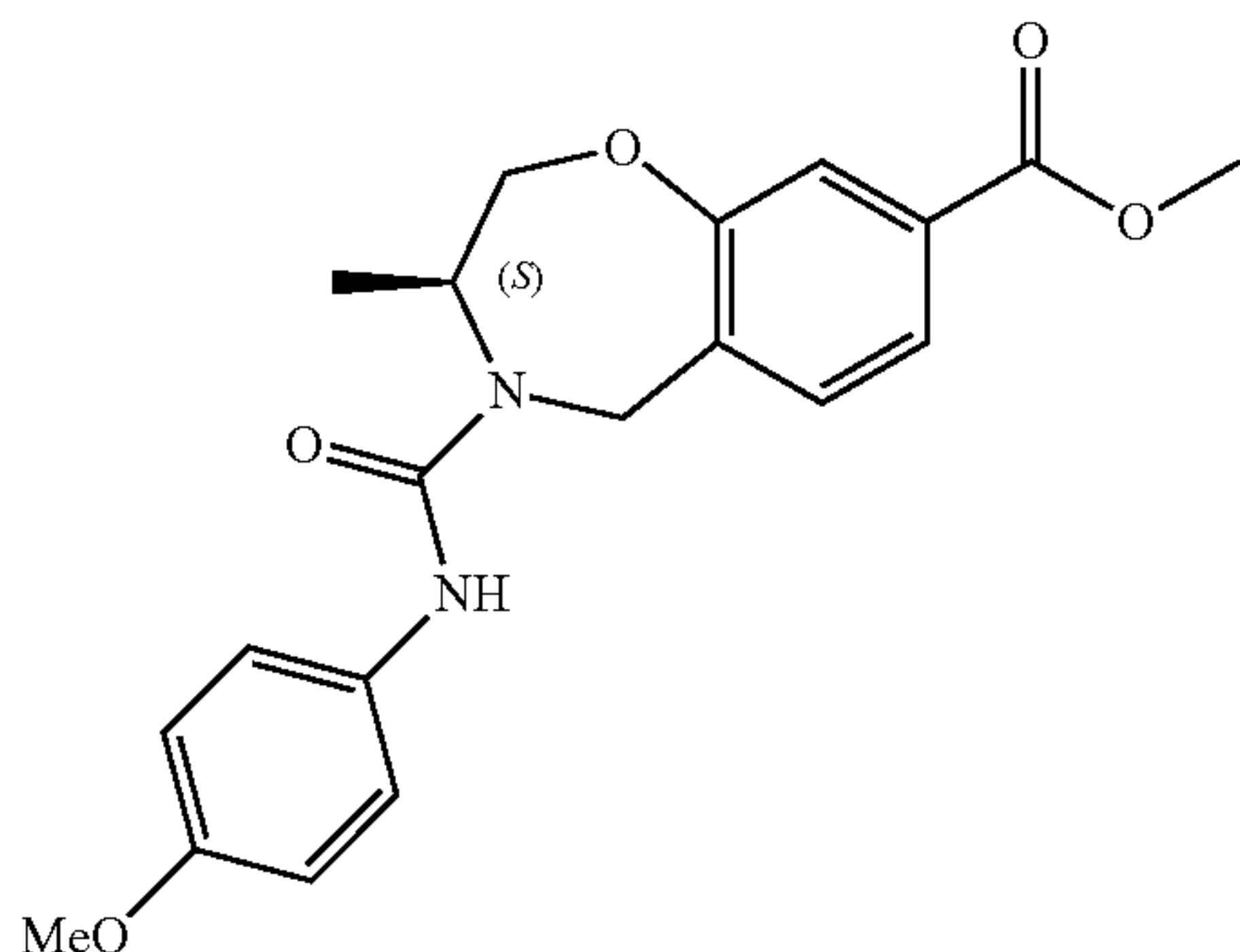
## 113

Step-2: Methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl (S)-3-bromo-4-(((1-hydroxypropan-2-yl)amino)methyl)benzoate (3.2 g, 10.59 mmol, 1 equiv) in isopropanol (35 mL), K<sub>2</sub>CO<sub>3</sub> (2.20 g, 15.92 mmol, 1.5 equiv) and CuI (610 mg, 3.20 mmol, 0.3 equiv). The resulting solution was stirred for 19 h at 110° C. in an oil bath. The resulting mixture was concentrated under vacuum, diluted with EtOAc (300 mL), and washed with H<sub>2</sub>O (3×100 mL). The organic phase was concentrated and the residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:4) to afford the title compound as a light yellow oil (1 g, 43% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 7.57-7.50 (m, 1H), 7.45 (s, 1H), 7.35-7.29 (m, 1H), 4.27-4.19 (m, 1H), 3.99-3.81 (m, 5H), 3.37-3.21 (m, 2H), 3.17-3.10 (s, 1H), 1.05-0.94 (d, J=6.4 Hz, 3H). MS: (ES, m/z): 222 [M+H]<sup>+</sup>.

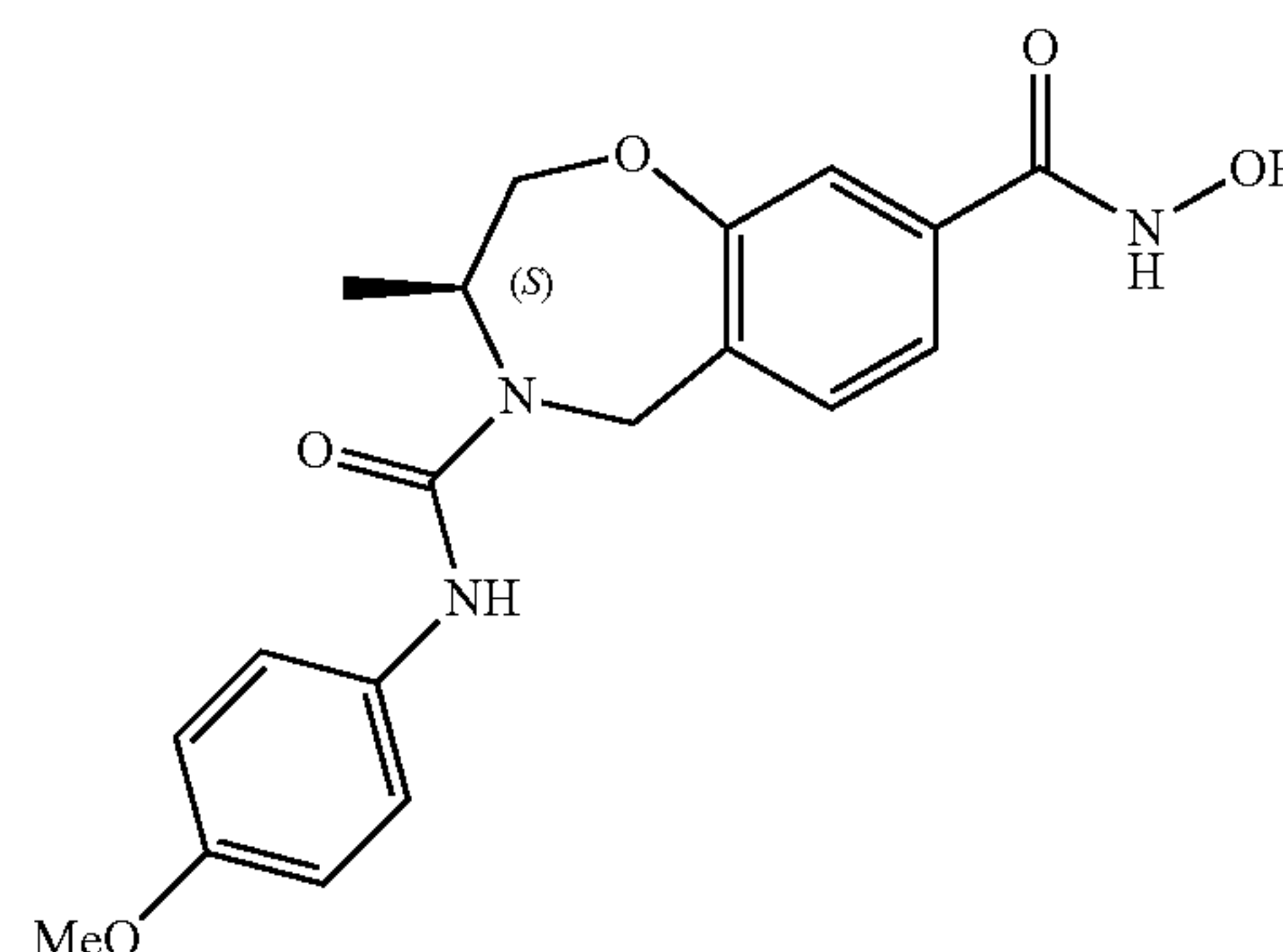
Step-3: Methyl (S)-4-((4-methoxyphenyl)carbamoyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



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Into a 25-mL flask, was placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), 1-isocyanato-4-methoxybenzene (100 mg, 0.67 mmol, 1.5 equiv), Et<sub>3</sub>N (150 mg, 1.48 mmol, 3 equiv) and 4-dimethylaminopyridine (50 mg, 0.41 mmol, 1 equiv). The resulting solution was stirred for 10 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a light yellow oil (30 mg, 18% yield). MS: (ES, m/z): 371 [M+H]<sup>+</sup>.

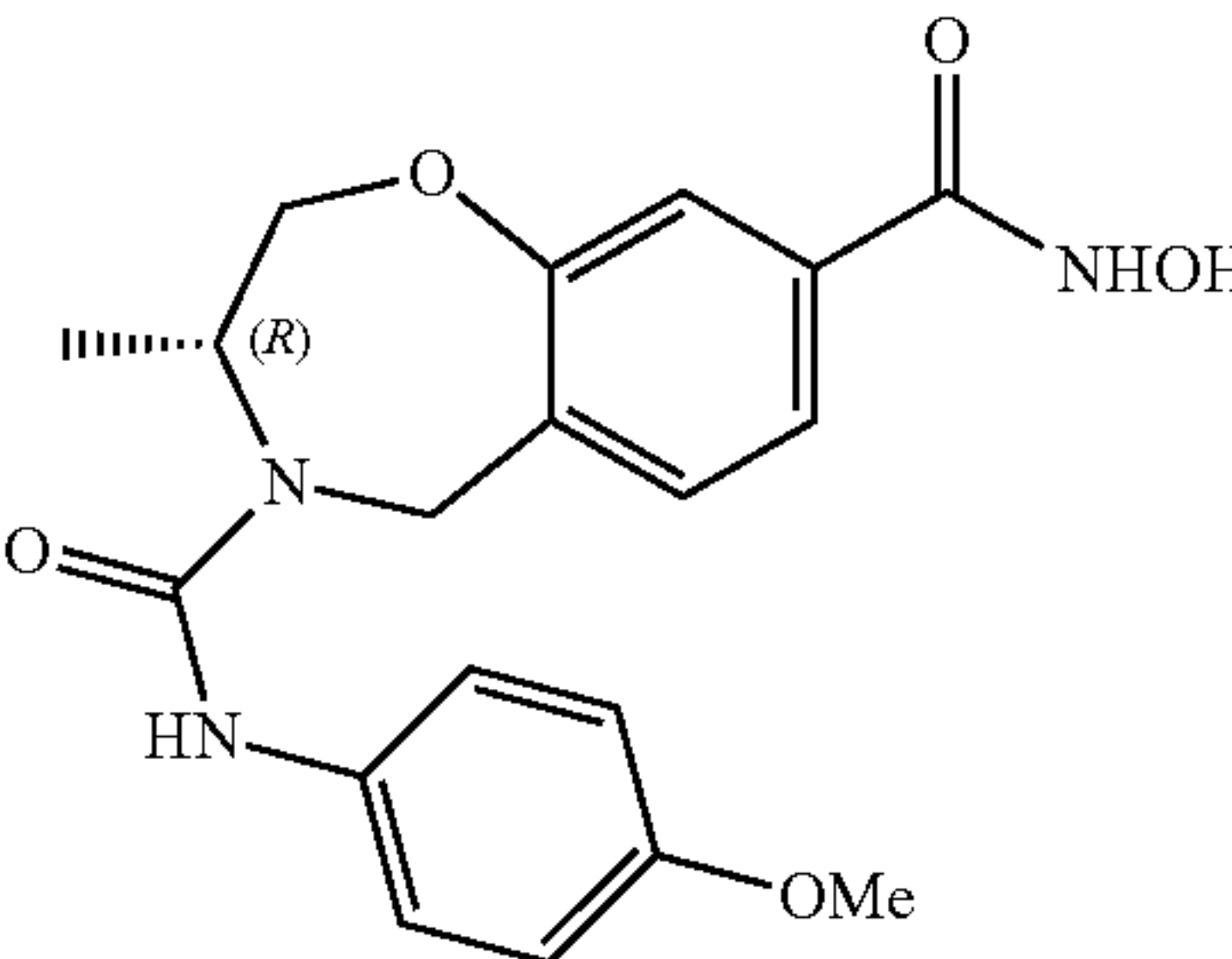
Step-4: (S)—N8-hydroxy-N4-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



Into a 10-mL vial, was placed a solution of methyl (S)-4-((4-methoxyphenyl)carbamoyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.27 mmol, 1 equiv) in THF/MeOH (3 mL, 4:1), followed by the addition of aq. 1N NaOH (0.54 mL, 2 equiv.) and NH<sub>2</sub>OH (50% in water, 0.54 mL, 30 equiv.). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge XP C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 13% B to 46% B in 9 min; Detector, UV 254, 220 nm) to afford the title compound as a pink solid (81 mg, 81% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.12 (br s, 1H), 8.19 (br s, 1H), 7.31-7.25 (m, 4H), 7.19 (s, 1H), 6.80-6.77 (m, 2H), 4.86-4.80 (m, 1H), 4.67-4.61 (m, 2H), 4.29-4.13 (m, 2H), 3.68 (s, 3H), 1.23-1.15 (m, 3H). MS: (ES, m/z): 372 [M+H]<sup>+</sup>.



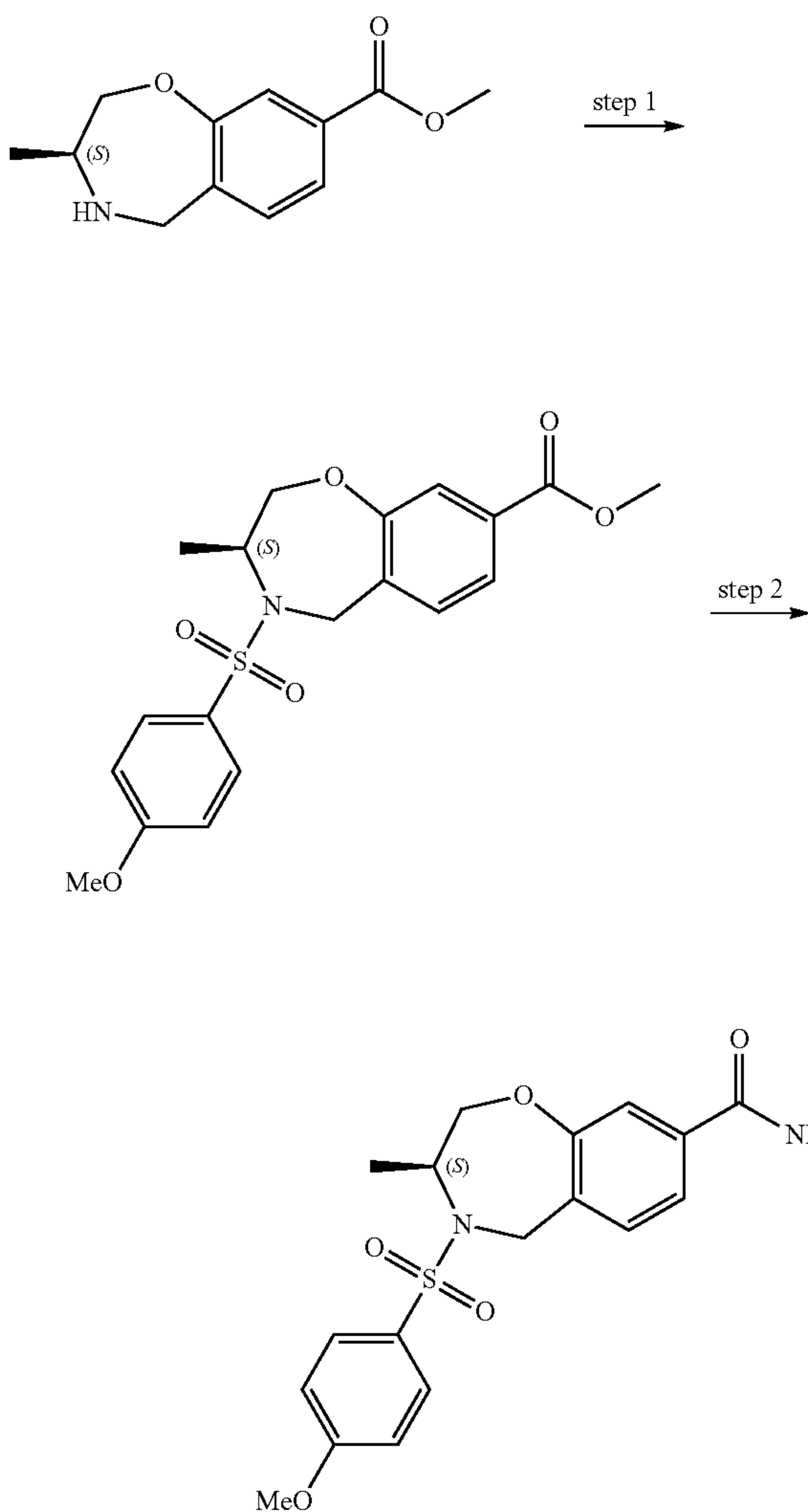
TABLE 14

The following compound was prepared according to the method of Example 35, using (R)-2-aminopropan-1-ol.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 372 [M + H] <sup>+</sup>	11.11 (br s, 1H), 8.18 (s, 1H), 7.33-7.24 (m, 4H), 7.18 (s, 1H), 6.80-6.76 (m, 2H), 4.85-4.80 (m, 1H), 4.69-4.61 (m, 2H), 4.27-4.15 (m, 2H), 3.68 (s, 3H), 1.16-1.15 (m, 3H)

## Example 36

Preparation of (S)—N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

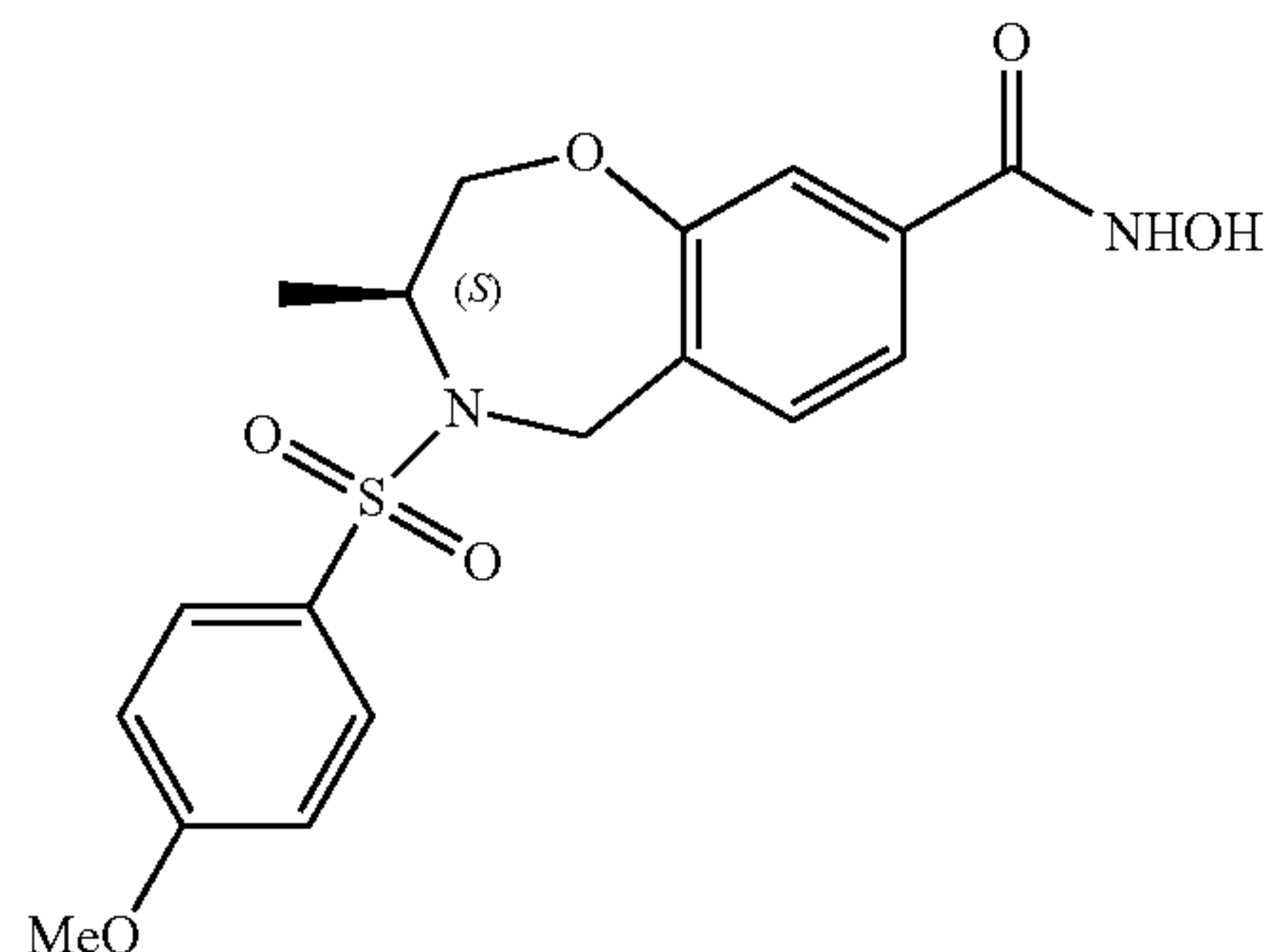
Step-1: Methyl (S)-4-((4-methoxyphenyl)sulfonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL), Et<sub>3</sub>N (137 mg, 1.35 mmol, 3 equiv), 4-dimethylaminopyridine (110 mg, 0.90 mmol, 2 equiv) and 4-methoxybenzene-1-sulfonyl chloride (234 mg, 1.13 mmol, 2.50 equiv). The resulting solution was stirred for 17 h at room temperature and then concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (10 mL), extracted with EtOAc (20 mL) and the organic layer concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:2) to afford the title compound as a light yellow oil (90 mg, 51% yield). MS: (ES, m/z): 392 [M+H]<sup>+</sup>.

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Step-2: (S)—N-Hydroxy-4-((4-methoxyphenyl)sulfonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed methyl (S)-4-((4-methoxyphenyl)sulfonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (90 mg, 0.23 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL). To this was added aq. 1N NaOH (0.46 mL, 2 equiv) and NH<sub>2</sub>OH (50% in water, 0.46 mL, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge XP C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 5% B to 55% B in 7 min; Detector, UV 254, 220 nm) to afford the title compound as an off-white solid (64 mg, 71% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.07 (br s, 1H), 7.36-7.33 (m, 2H), 7.28-7.25 (m, 1H), 7.21-7.18 (m, 1H), 6.80 (s, 1H), 6.75-6.72 (m, 2H), 4.90-4.84 (d, J=17.4 Hz, 1H), 4.60-4.54 (d, J=17.4 Hz, 1H), 4.32-4.29 (m, 1H), 4.17-4.13 (m, 1H), 4.09-3.99 (m, 1H), 3.71 (m, 4H), 1.13-1.11 (m, J=6.6 Hz, 3H). MS: (ES, m/z): 393 [M+H]<sup>+</sup>.

TABLE 15

The following compound was prepared according to the method of Example 36, using methyl (R)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate.

Structure	Found	
	M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 393 [M + H] <sup>+</sup>	11.07 (br s, 1H), 8.98 (s, 1H), 7.36-7.33 (m, 2H), 7.28-7.25 (m, 1H), 7.20-7.18 (m, 1H), 6.80 (s, 1H), 6.79-6.72 (m, 2H), 4.89-4.85 (m, 1H), 4.59-4.55 (m, 1H), 4.31-4.26 (1, 2H), 4.16-4.10 (m, 1H), 4.02-3.98 (m, 1H), 3.71 (s, 3H), 1.13-1.06 (m, 3 H)

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Example 37

Preparation of (S)—N-hydroxy-4-(4-methoxybenzyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

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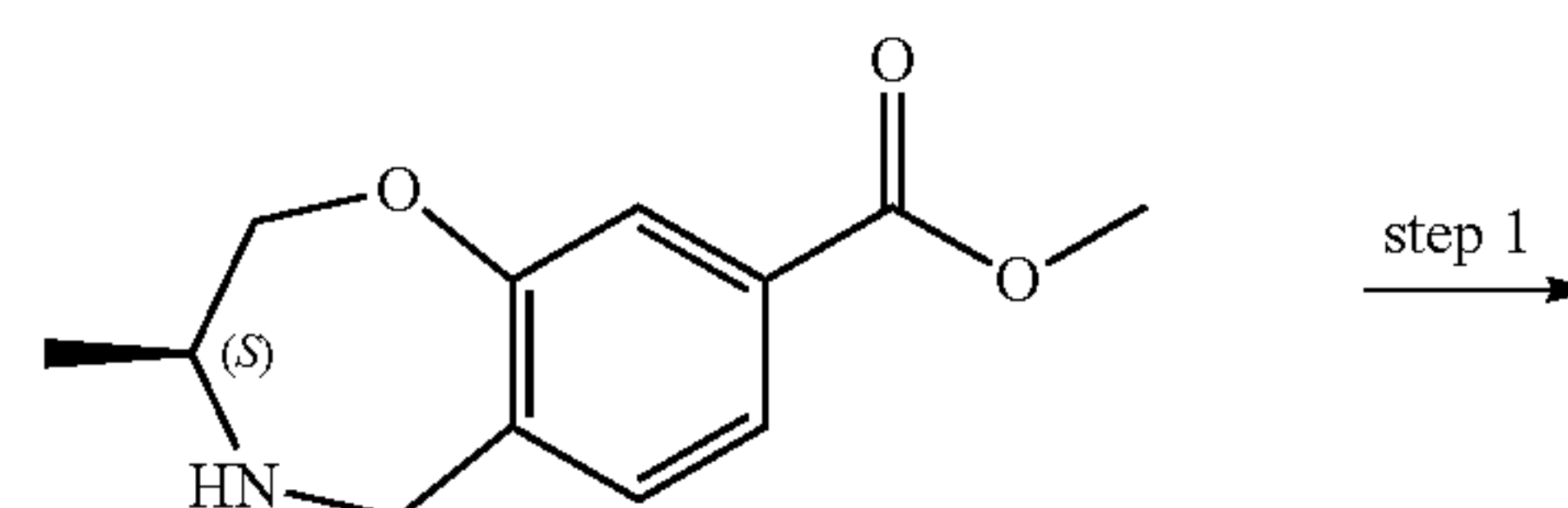
20

25

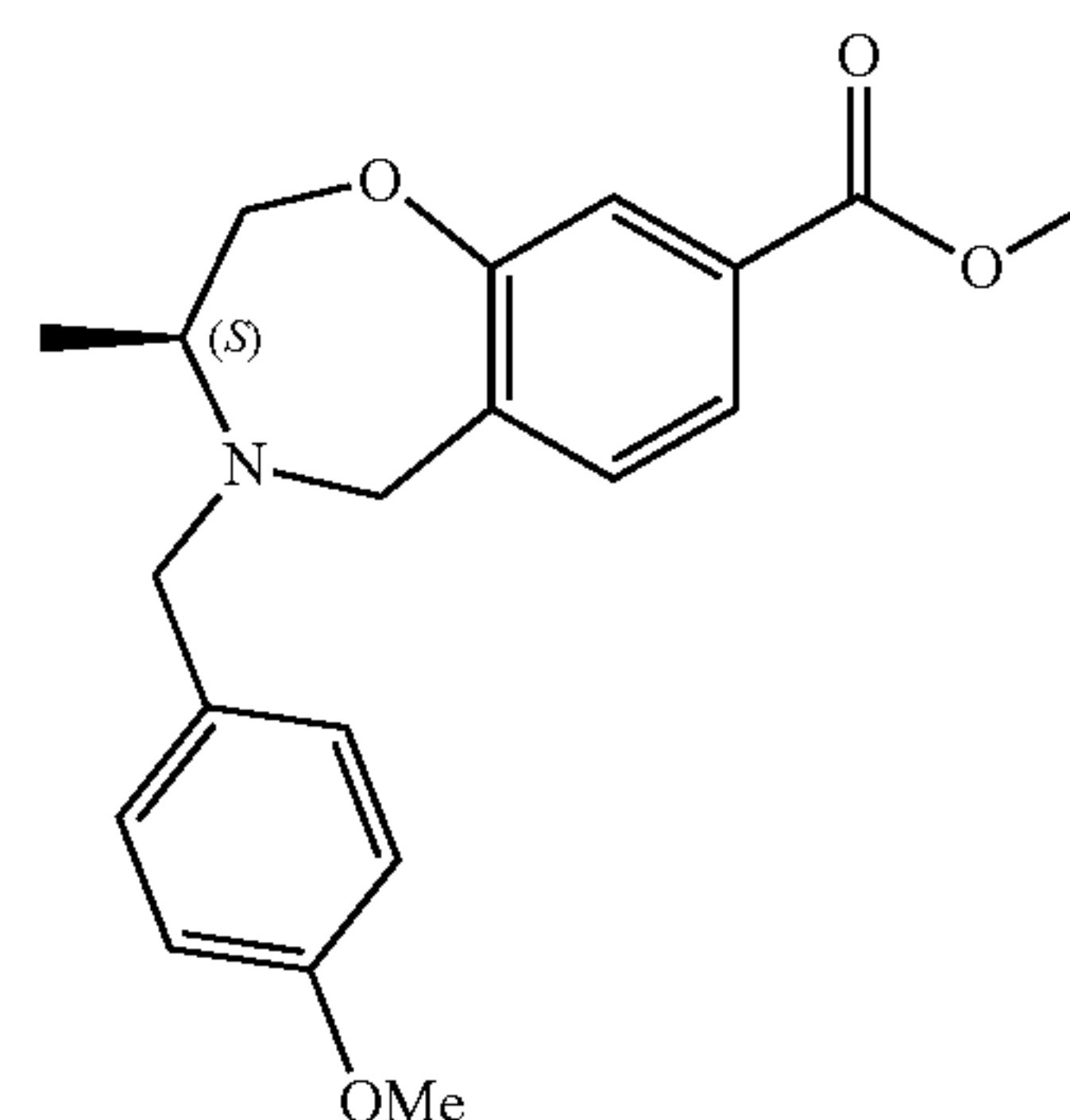
30

35

40



step 1

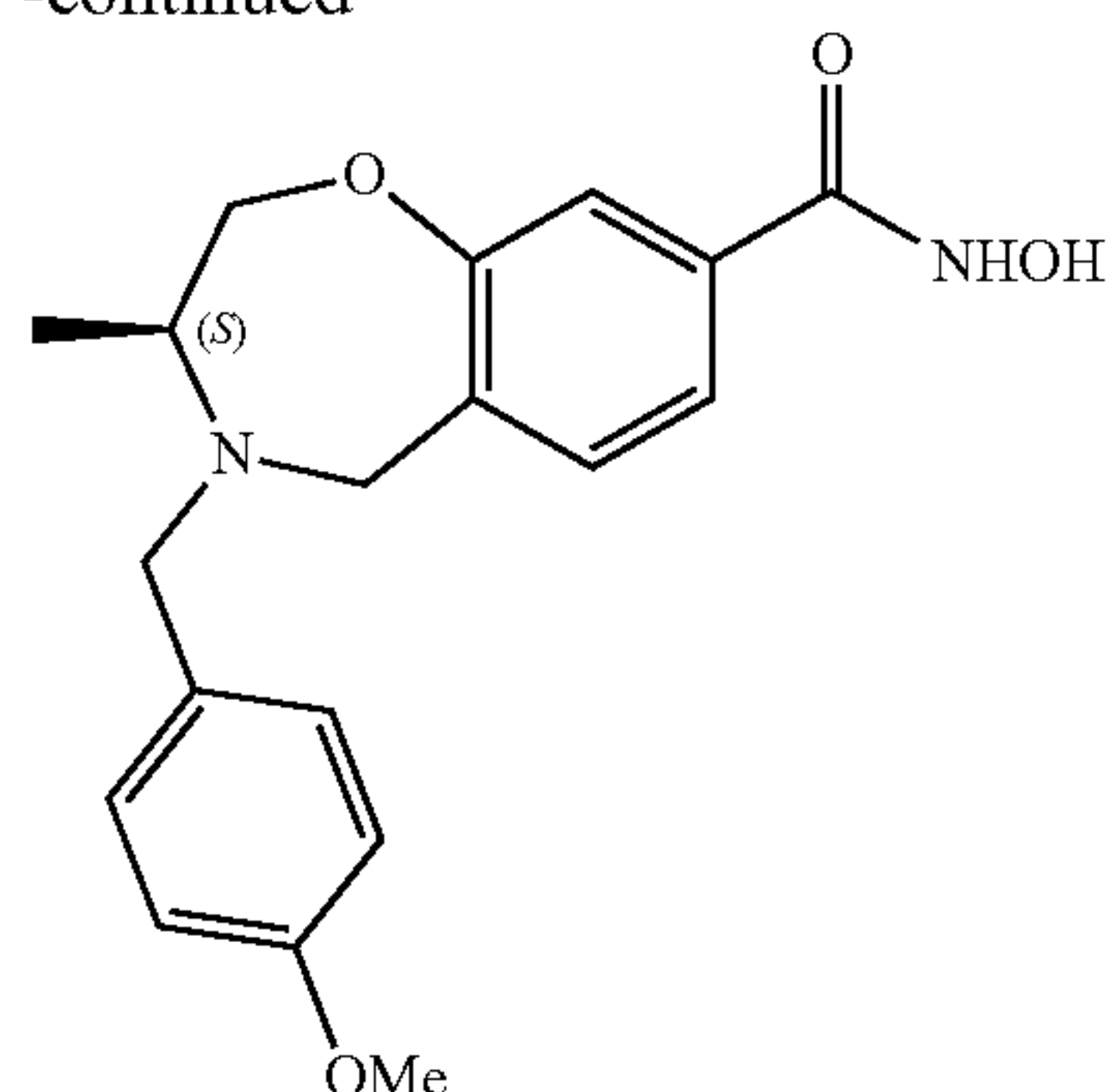


step 2

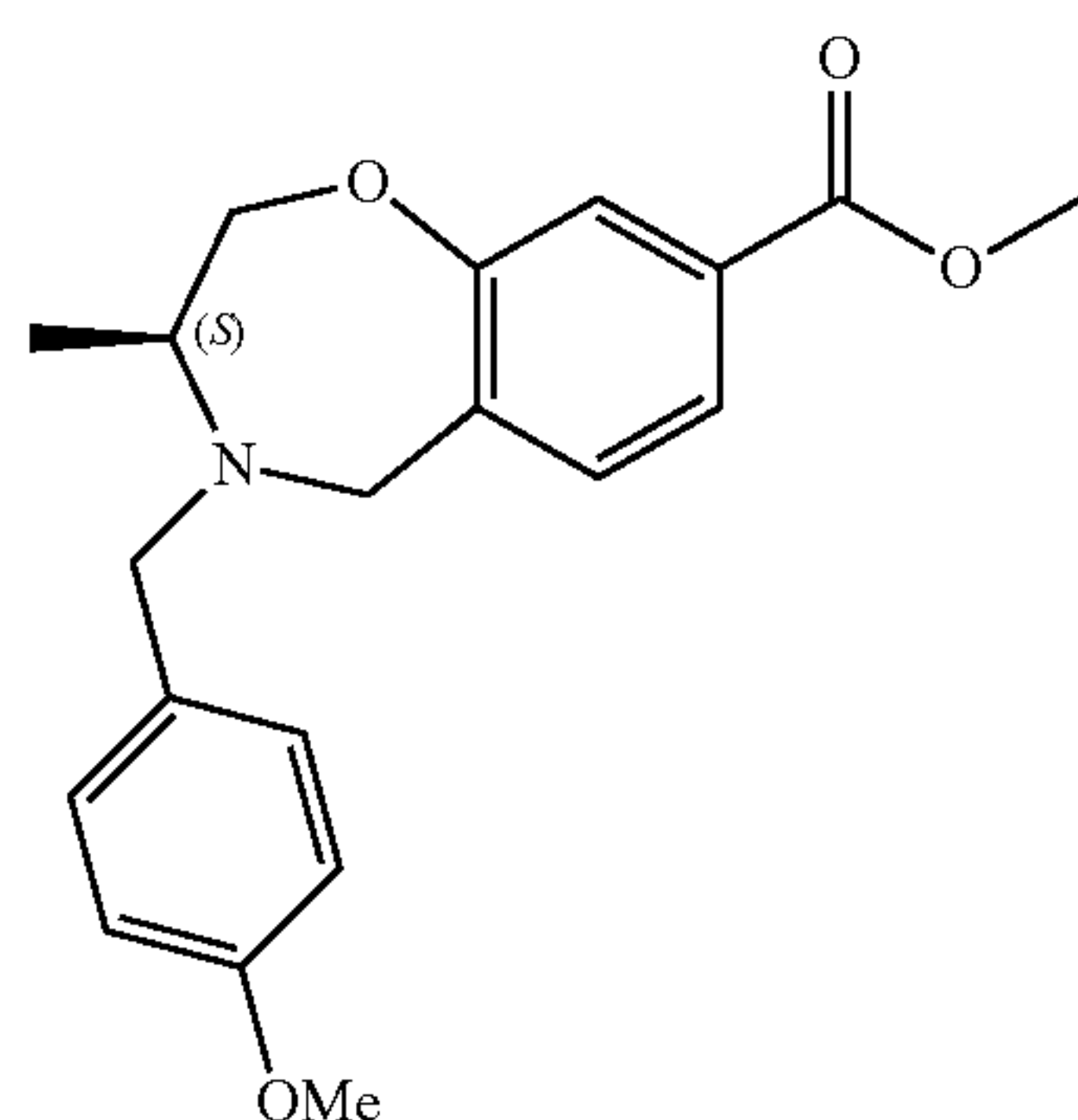


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-continued



Step-1: Methyl (S)-4-(4-methoxybenzyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

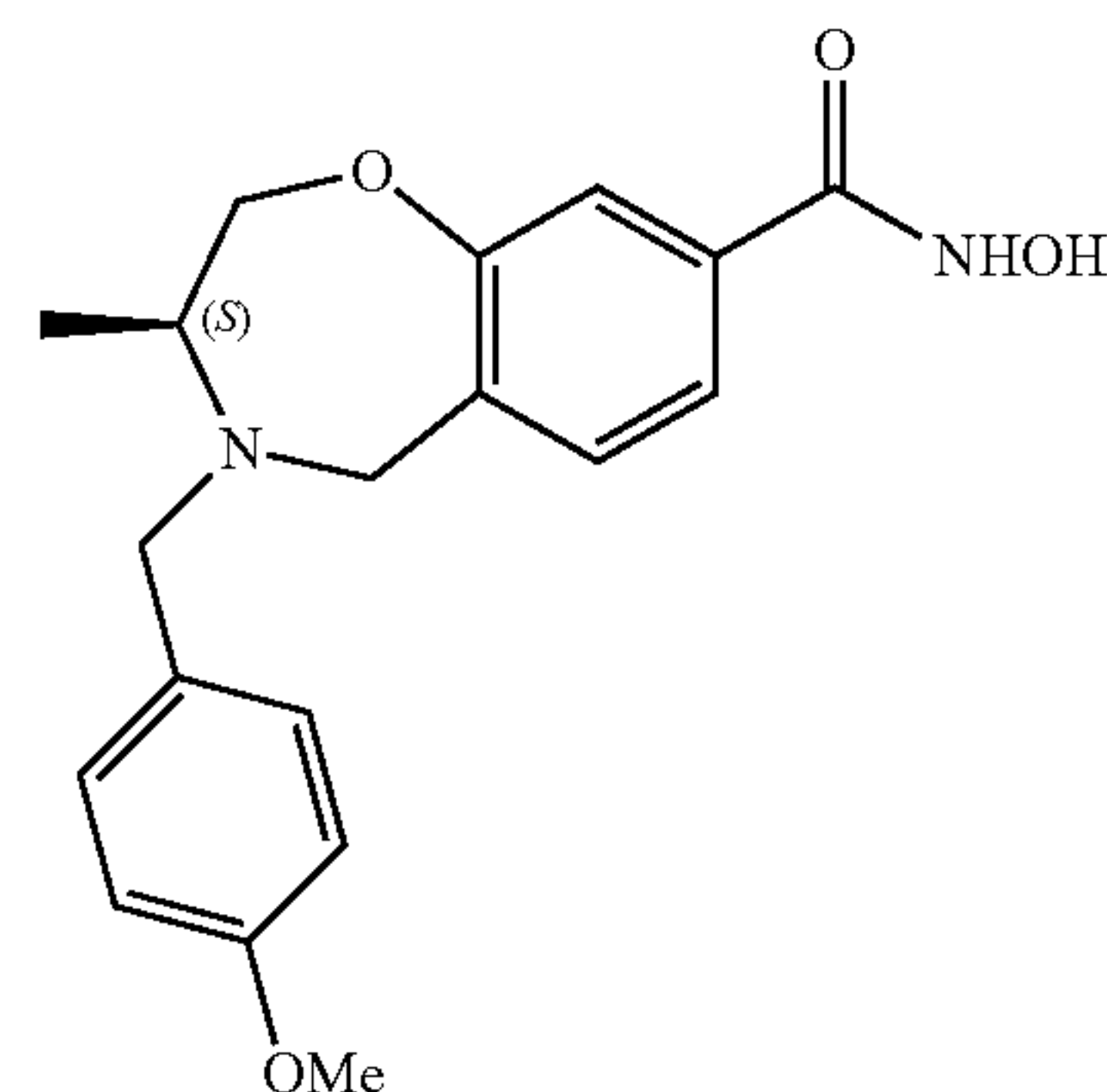


Into a 8-mL vial, was placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv) in THF (3 mL). This was followed by the addition of sodium hydride (90 mg, 3.75 mmol, 5 equiv, 60% dispersion in oil) and 1-(bromomethyl)-4-methoxybenzene (91 mg, 0.45 mmol, 1 equiv). The

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resulting solution was stirred for 17 h at room temperature. The reaction was then quenched by the addition of H<sub>2</sub>O (2 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a light yellow oil (68 mg, 44% yield). MS: (ES, m/z): 342 [M+H]<sup>+</sup>.

Step-2: (S)—N-Hydroxy-4-(4-methoxybenzyl)-3-methyl-2,3,4,5-tetrahydrobenzo [f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed methyl (S)-4-(4-methoxybenzyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (67.6 mg, 0.20 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL). To this was added aq. 1N NaOH (0.40 ml, 2 equiv) and NH<sub>2</sub>OH (50% in water, 0.40 mL, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge XP C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 5% B to 25% B in 7 min; Detector, UV 254, 220 nm) to afford the title compound as a brown solid (58 mg, 85% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.35 (br, 1H), 10.65 (br, 1H), 7.52-7.25 (m, 5H), 7.02-6.99 (m, 2H), 4.89-4.28 (m, 6H), 3.86-3.67 (m, 4H), 1.48-1.46 (d, J=6 Hz, 3H). MS: (ES, m/z): 343 [M+H]<sup>+</sup>.

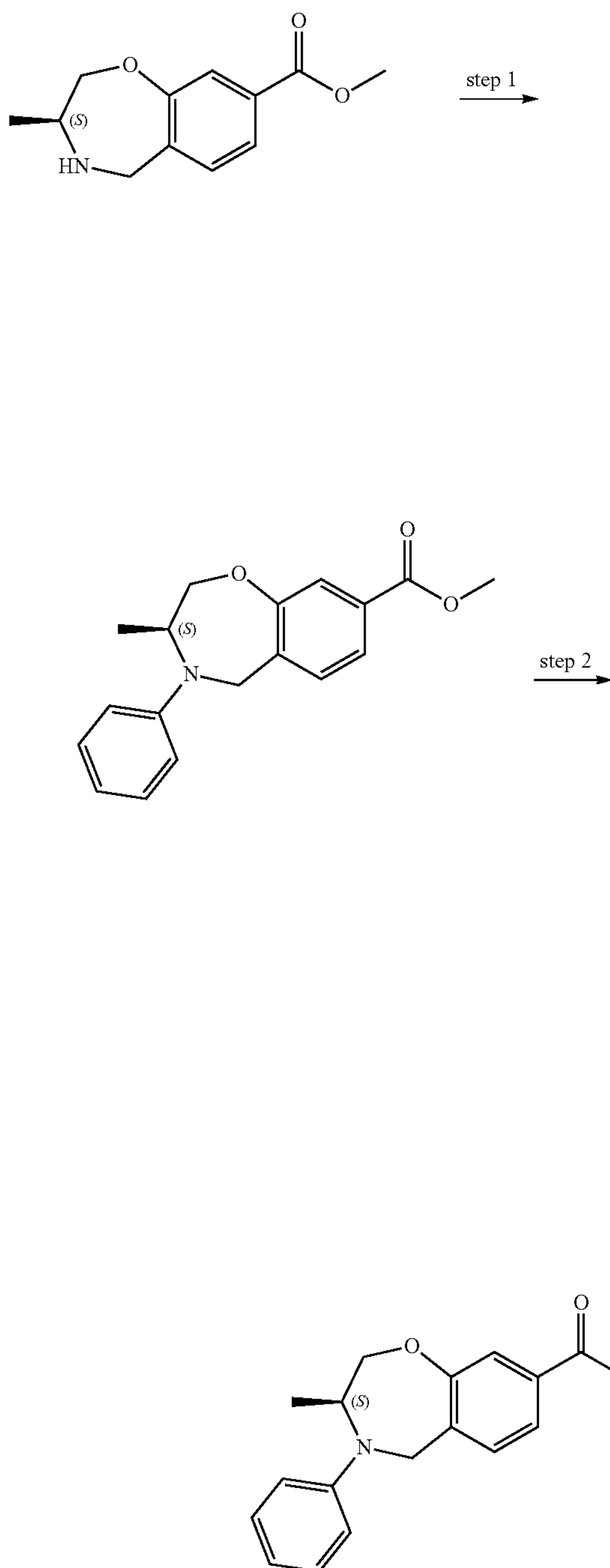
TABLE 16

The following compound was prepared according to the method of Example 37, using methyl (R)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 343 [M + H] <sup>+</sup>	11.31 (s, 1H), 10.83-10.06 (br, 1H), 9.73-8.57 (br, 1H), 7.51-7.33 (m, 5H), 7.13-6.92 (m, 2H), 5.13-3.96 (m, 7H), 3.78 (s, 3H), 1.47 (s, 3H)

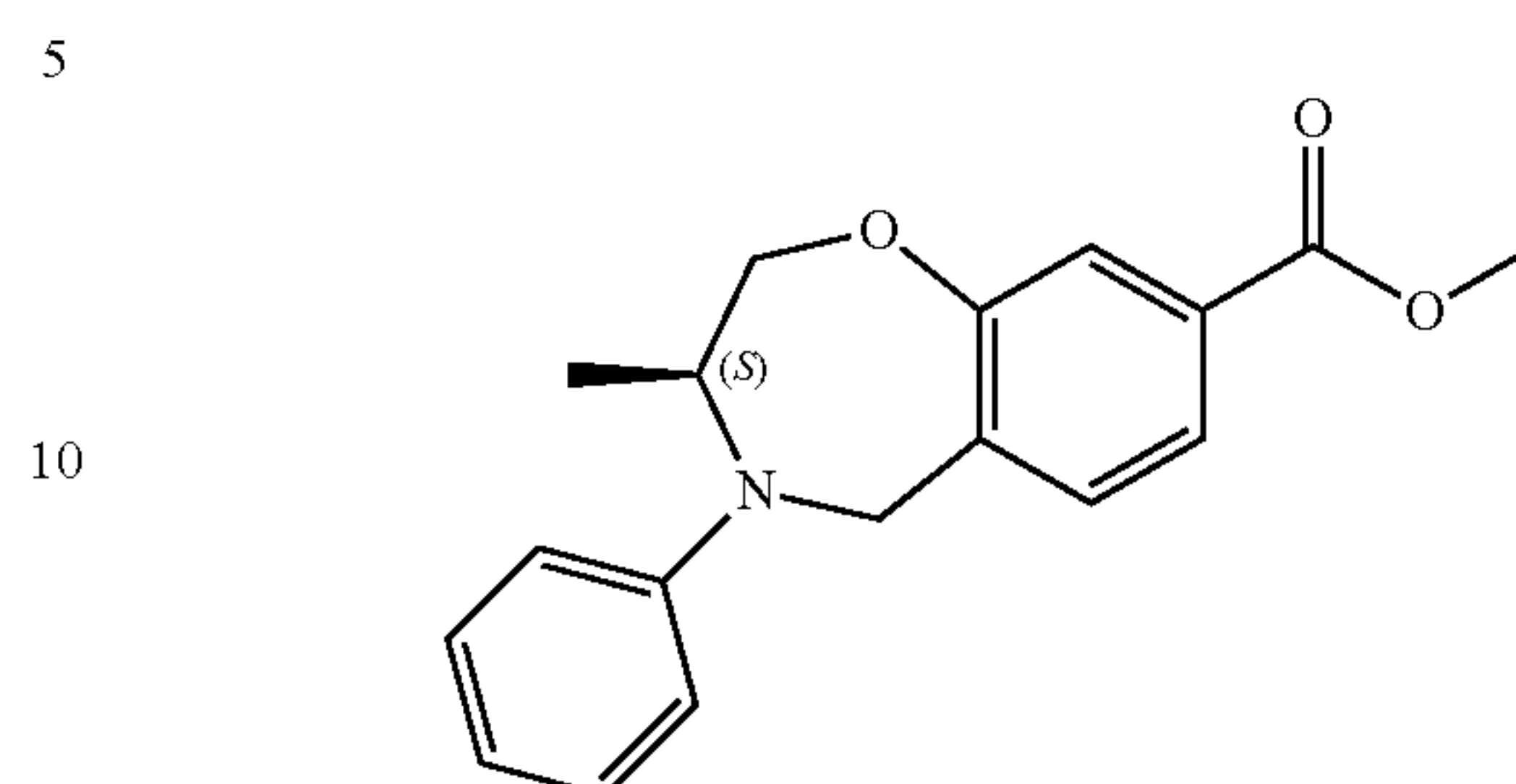
**121**

## Example 38

Preparation of (S)—N-hydroxy-3-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

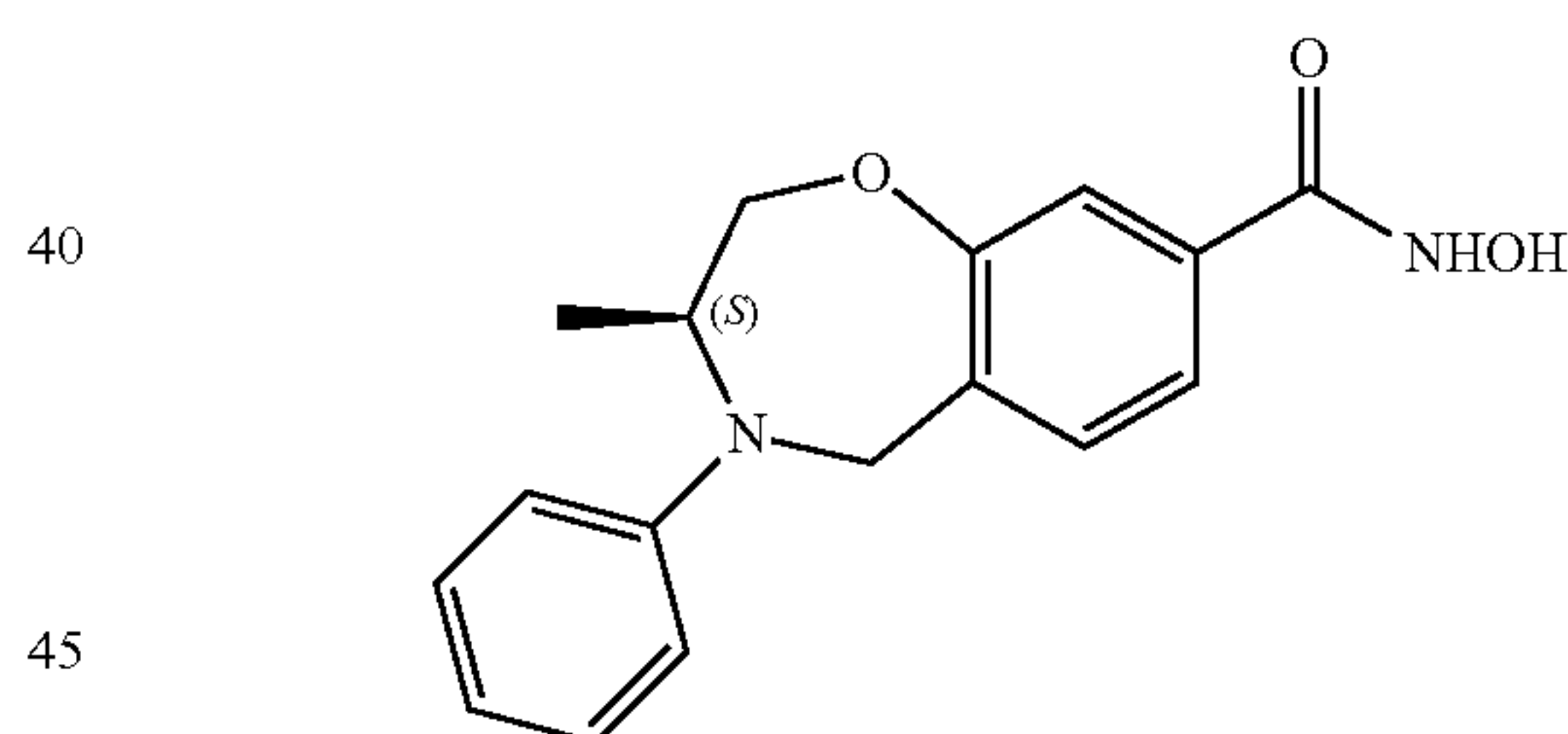
**122**

Step-1: Methyl (S)-3-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 25-mL vial purged and maintained with an inert atmosphere of nitrogen, were placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (300 mg, 1.36 mmol, 1 equiv) in 1,4-dioxane (8 mL), iodobenzene (827 mg, 4.05 mmol, 3 equiv), Xantphos (312 mg, 0.54 mmol, 0.4 equiv), Cs<sub>2</sub>CO<sub>3</sub> (1.33 g, 4.05 mmol, 3 equiv) and Pd(OAc)<sub>2</sub> (61 mg, 0.27 mmol, 0.2 equiv). The resulting solution was stirred for 21 h at 110° C. in an oil bath. The resulting mixture was concentrated under vacuum and the residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a light yellow oil (41 mg, 10% yield). MS: (ES, m/z): 298 [M+H]<sup>+</sup>.

Step-2: (S)—N-hydroxy-3-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed methyl (S)-3-methyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (41 mg, 0.14 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL). To this was added aq. 1N NaOH (0.28 mL, 2 equiv) and NH<sub>2</sub>OH (50% in water, 0.28 mL, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: XBridge XPC18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 5% B to 80% B in 7 min; Detector, UV 254, 220 nm) to afford the title compound as a light brown solid (13 mg, 33% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.10-11 (br s, 1H), 7.49-7.46 (m, 1H), 7.34-7.32 (m, 1H), 7.10-7.04 (m, 3H), 6.66-6.64 (m, 2H), 6.56-6.51 (m, 1H), 5.03-4.97 (d, J=17.4 Hz, 1H), 4.41-4.20 (m, 4H), 1.20-1.18 (d, J=5.7 Hz, 3H). MS: (ES, m/z): 299 [M+H]<sup>+</sup>.

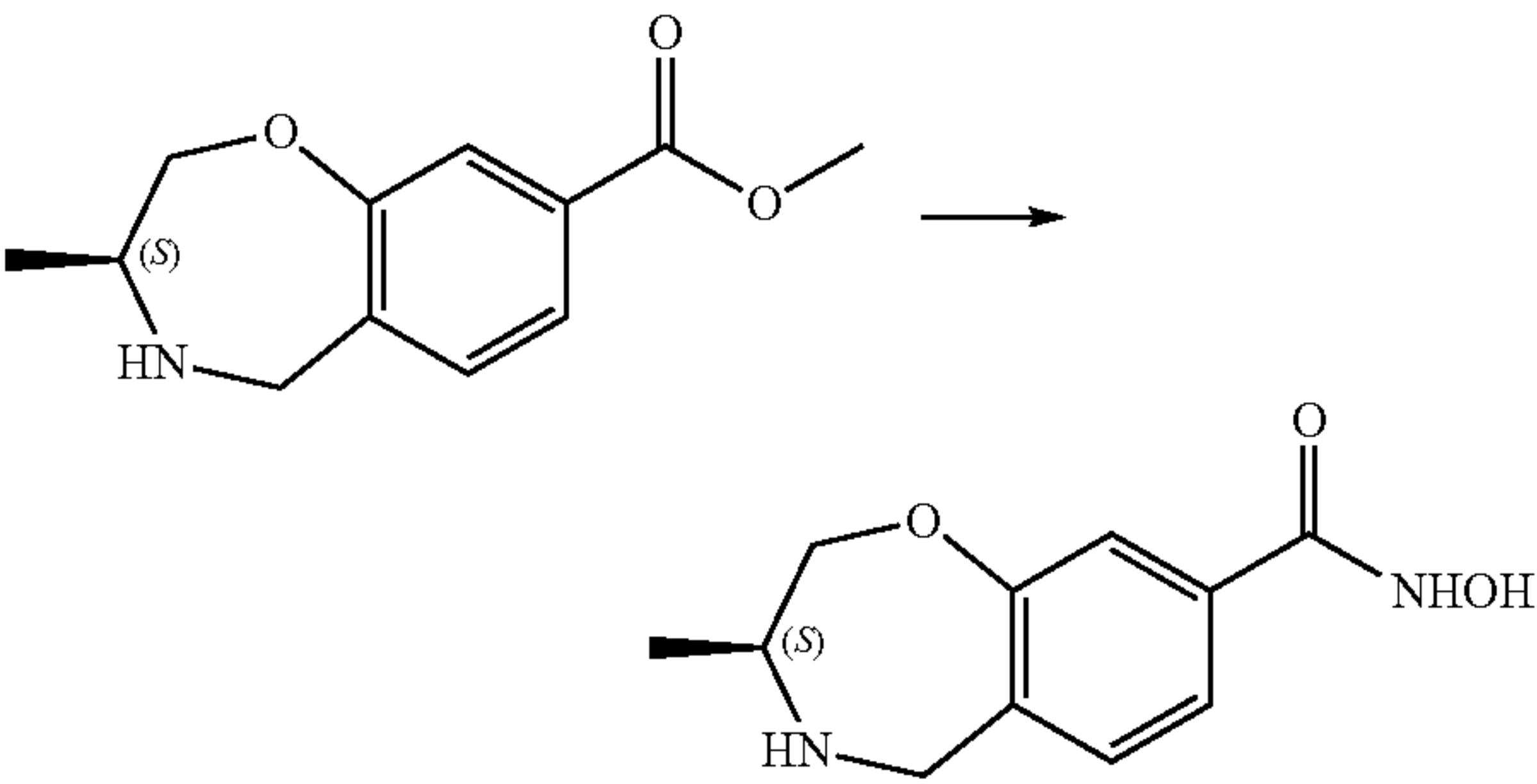


TABLE 17

The following compound was prepared according to the method of Example 38, using methyl (R)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 11.09 (br s, 1H), 7.49-7.47 (m, 1H), 7.34-7.32 (m, 1H), 299 7.10-7.05 (m, 3H), 6.66-6.64 (m, 2H), 6.56-6.52 (m, 1H), [M + H] <sup>+</sup> 5.30-4.95 (d, J = 17.4 Hz, 1H), 4.49-4.20 (m, 4H), 1.23-1.18 (d, J = 5.7 Hz, 3H)	

Example 39

Preparation of (S)—N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo [f][1,4]oxazepine-8-carboxamide



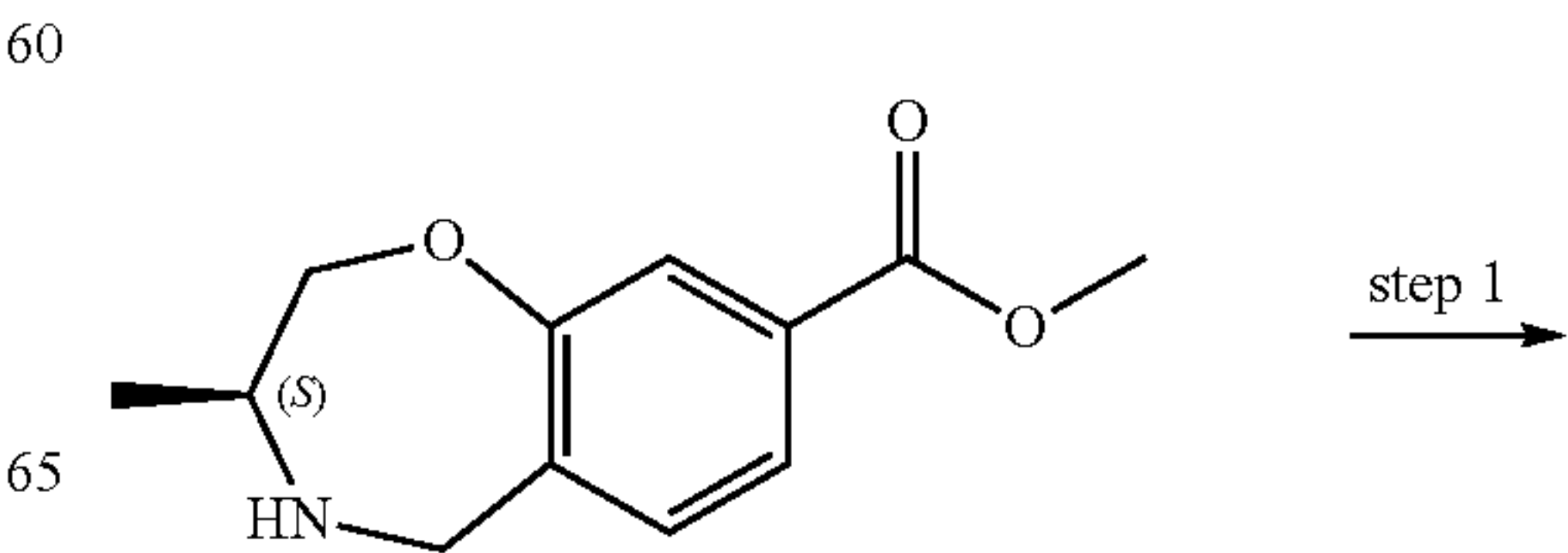
Into a 8-mL vial, was placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (50 mg, 0.23 mmol, 1 equiv) in THF/MeOH (4:1, 1 mL), NH<sub>2</sub>OH (50% in water, 0.44 mL, 30 equiv) and aq. 1N NaOH (0.45 mL, 2 equiv). The resulting solution was stirred for 14 h at room temperature. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 4% B to 20% B in 7 min; Detector, UV 254, 220 nm) to afford the title compound as the TFA salt as a pink solid (9 mg, 11% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.31 (s, 1H), 9.12 (s, 3H), 7.53 (s, 2H), 7.44 (s, 1H), 4.42-4.33 (m, 3H), 3.79-3.74 (t, J=9.8 Hz, 2H), 1.24-1.23 (d, J=3.0 Hz, 3H). MS: (ES, m/z): 223 [M+H]<sup>+</sup>.

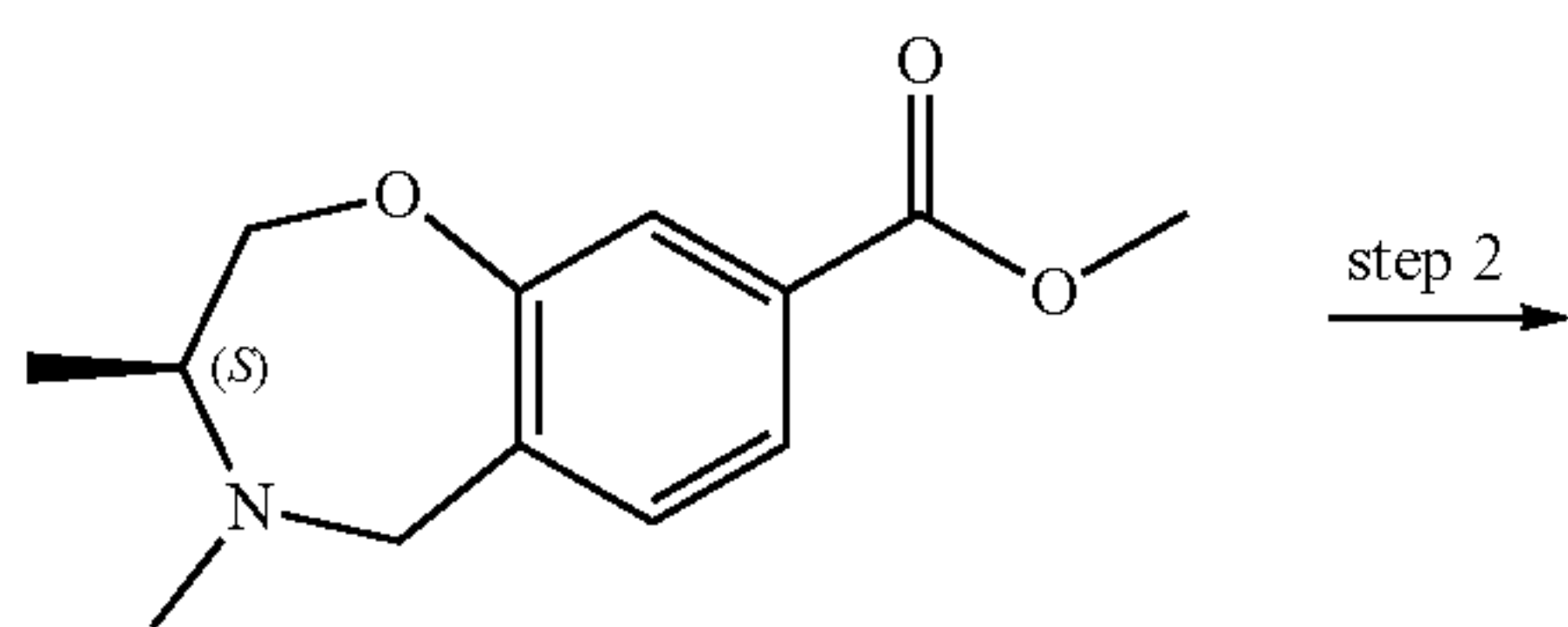
TABLE 18

The following compound was prepared according to the method of Example 39, using methyl (R)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 11.30 (s, 1H), 9.50-9.44 (s, 1H), 9.12-8.99 (s, 2H), 7.53-7.44 (d, J = 17.8 Hz, 3H), 4.43-4.33 (m, 3H), 3.79-3.75 (d, J = 20.4 Hz, 2H), 1.29-1.22 (s, 3H)	

Example 40

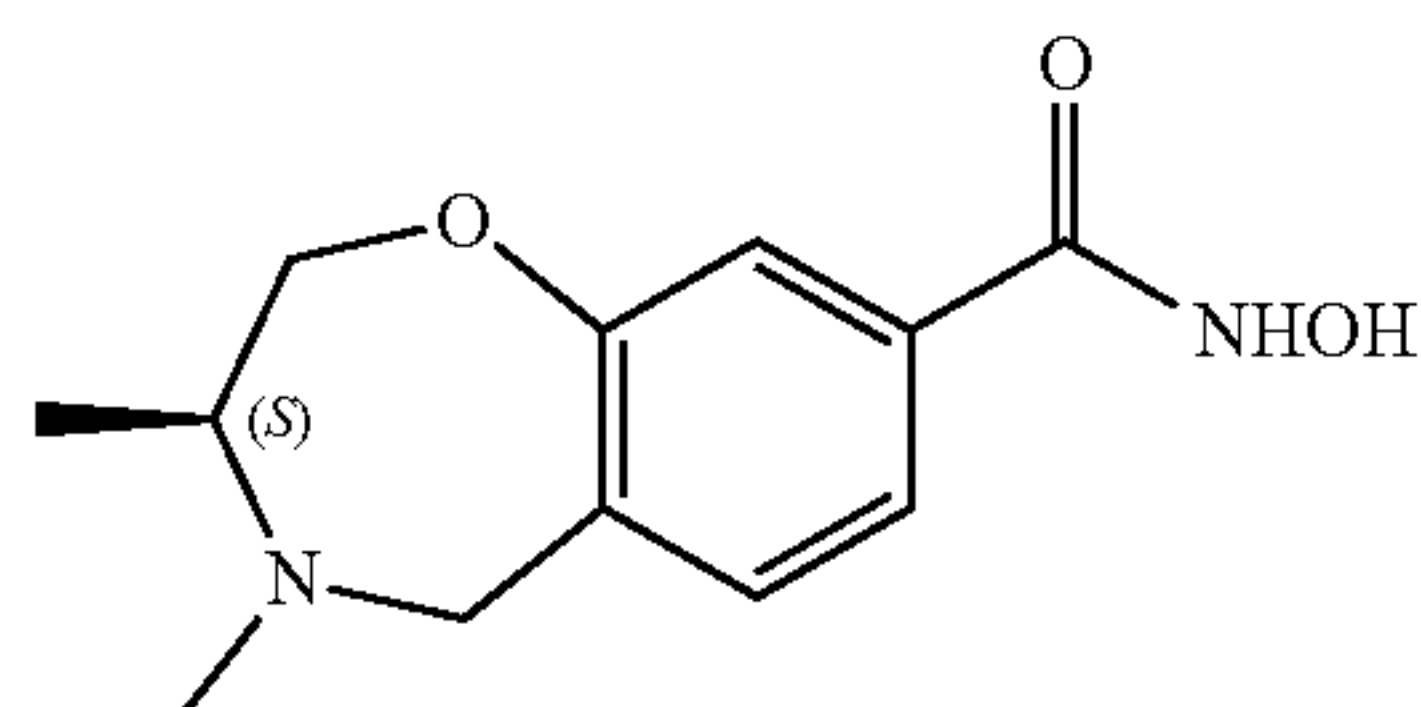
Preparation of (S)—N-hydroxy-3,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



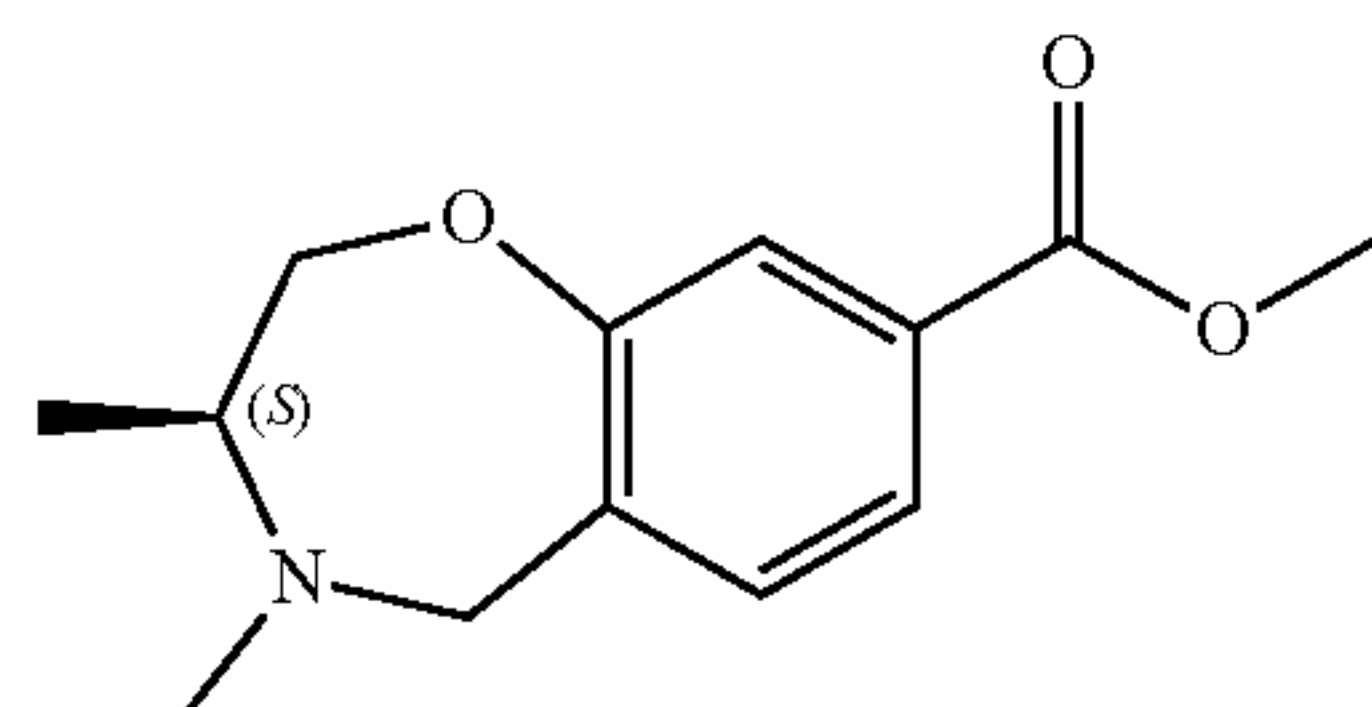
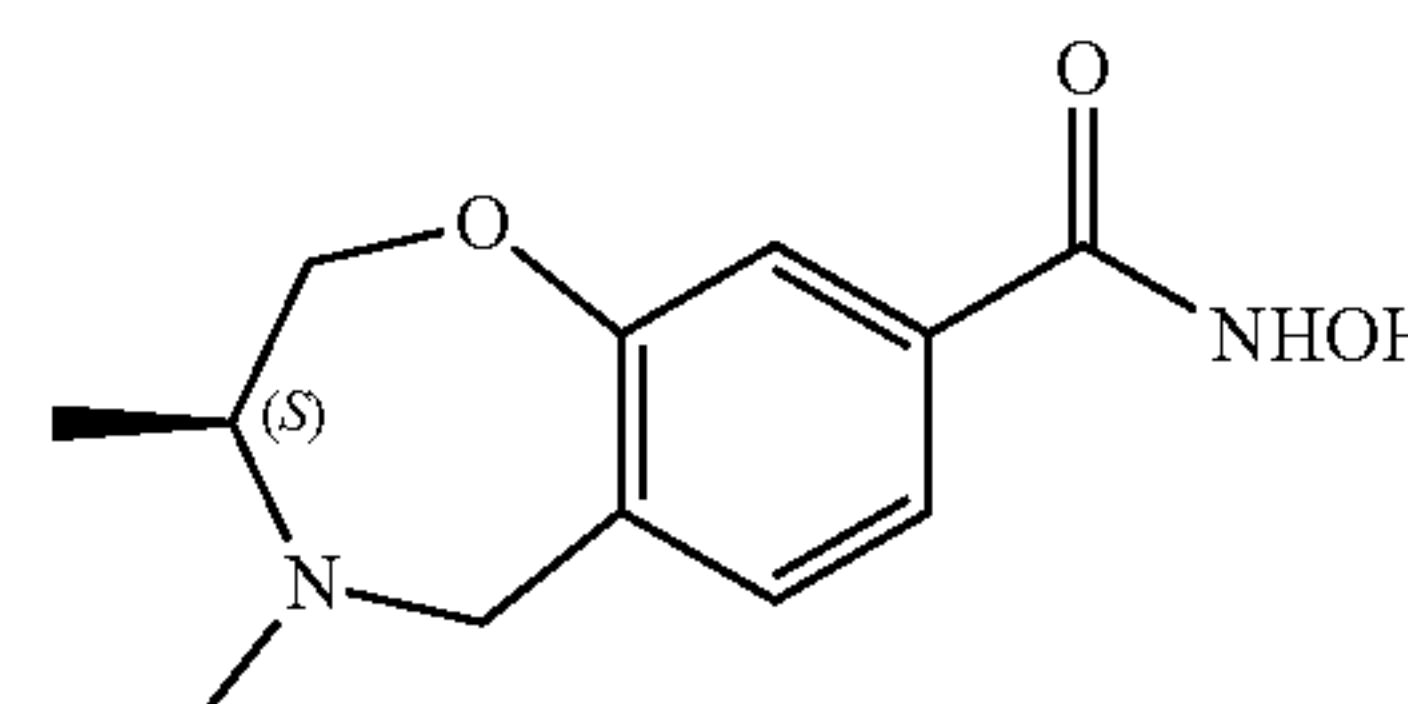
**125****126**

equiv) was added in portions at 0° C. The resulting solution was stirred for 18 h at room temperature. EtOAc was added and the resulting mixture was washed with H<sub>2</sub>O (2×20 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum to afford the title compound as a brown oil (70 mg, 66% yield). MS: (ES, m/z): 236 [M+H]<sup>+</sup>.

Step-2: (S)—N-Hydroxy-3,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Step-1: Methyl (S)-3,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv) in acetic acid (1.5 mL). This was followed by the addition of formaldehyde (41 mg, 1.37 mmol, 3 equiv). The mixture was stirred for 2 h at room temperature and NaBH(OAc)<sub>3</sub> (477 mg, 2.26 mmol, 5

Into a 8-mL vial, was placed a solution of methyl (S)-3,4-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (85 mg, 0.36 mmol, 1 equiv) in THF/MeOH (4:1, 1.5 mL), then aq. 1N NaOH (1.1 mL, 3 equiv) and NH<sub>2</sub>OH (50% in water, 0.72 mL, 30 equiv) were added simultaneously. The resulting solution was stirred for 15 h at room temperature. The crude product was purified by Prep-HPLC (Column: Atlantis T3 C18, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 2% B to 2% B in 13 min; Detector, UV 254, 220 nm) to afford the title compound as a TFA salt as an orange oil (9 mg, 7% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.31 (s, 1H), 10.08-10.06 (s, 1H), 9.14 (s, 1H), 7.55-7.43 (m, 3H), 4.63-4.41 (m, 2H), 4.16-4.10 (m, 2H), 3.84-3.61 (s, 1H), 2.85 (s, 1H), 2.67-2.64 (s, 2H), 1.54-1.29 (m, 3H). MS: (ES, m/z): 237 [M+H]<sup>+</sup>.

TABLE 19

The following compound was prepared according to the method of Example 40, using methyl (R)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate.

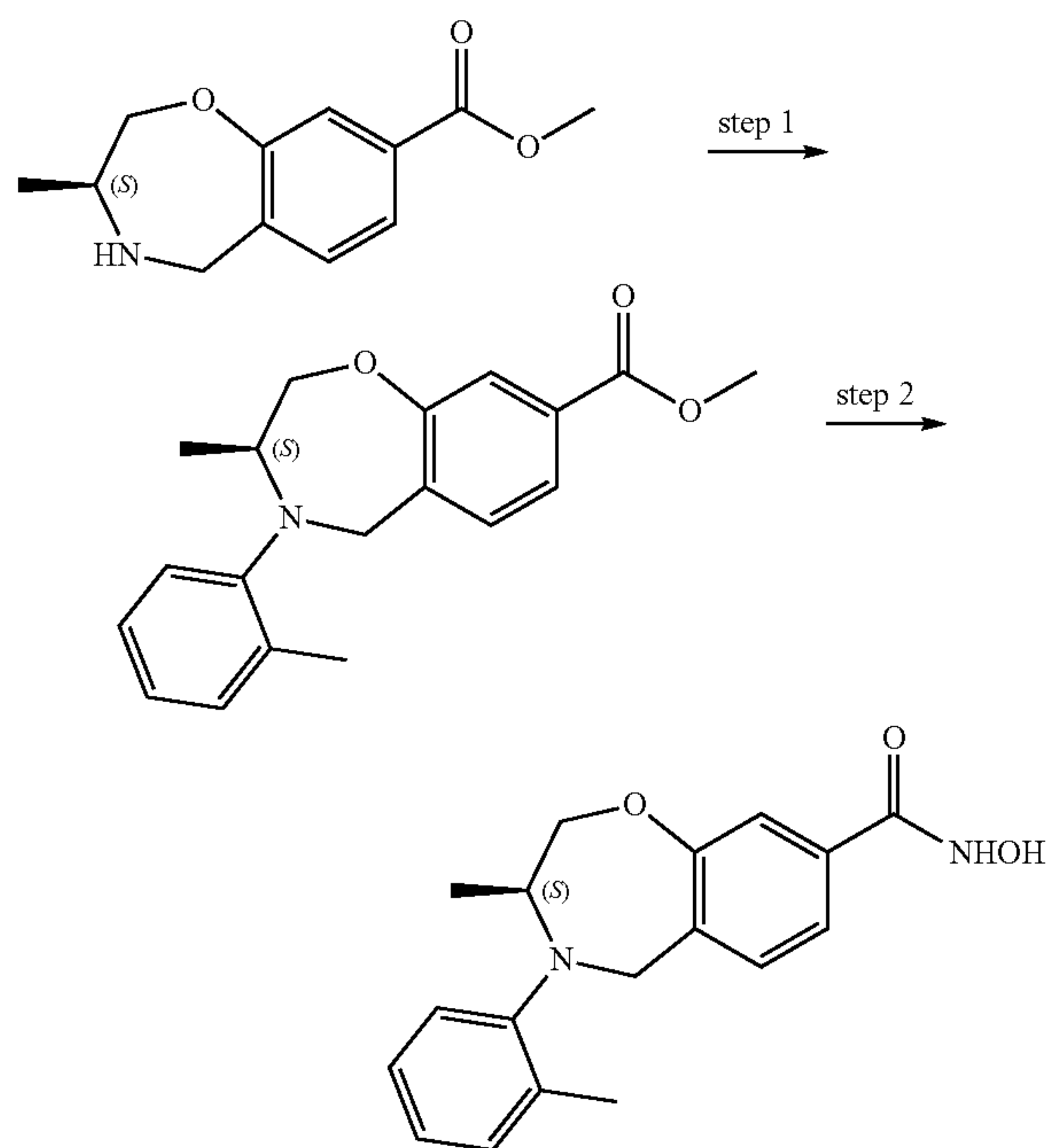
Structure	Found	
	M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 237	11.31 (s, 1H), 10.67-10.23 (br, 1H), 9.14 (br, 1H), 7.54-7.43 (m, 3H), 4.70-4.51 (m, 2H), 4.37-3.70 (m, 3H), 2.94-2.59 (m, 3H), 1.40-1.27 (d, J = 52.7, 3H)



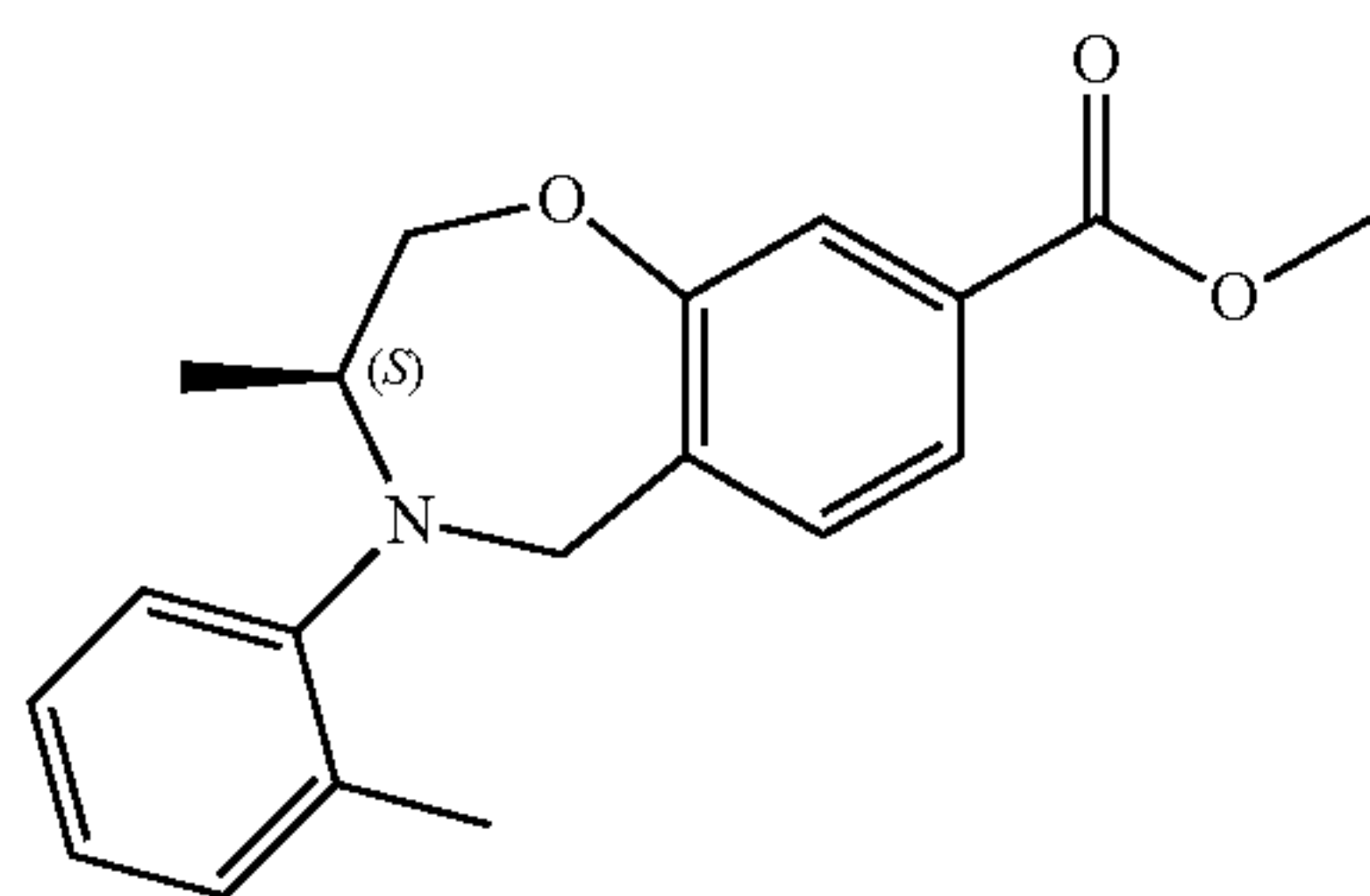
## 127

## Example 41

Preparation of (S)—N-hydroxy-3-methyl-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



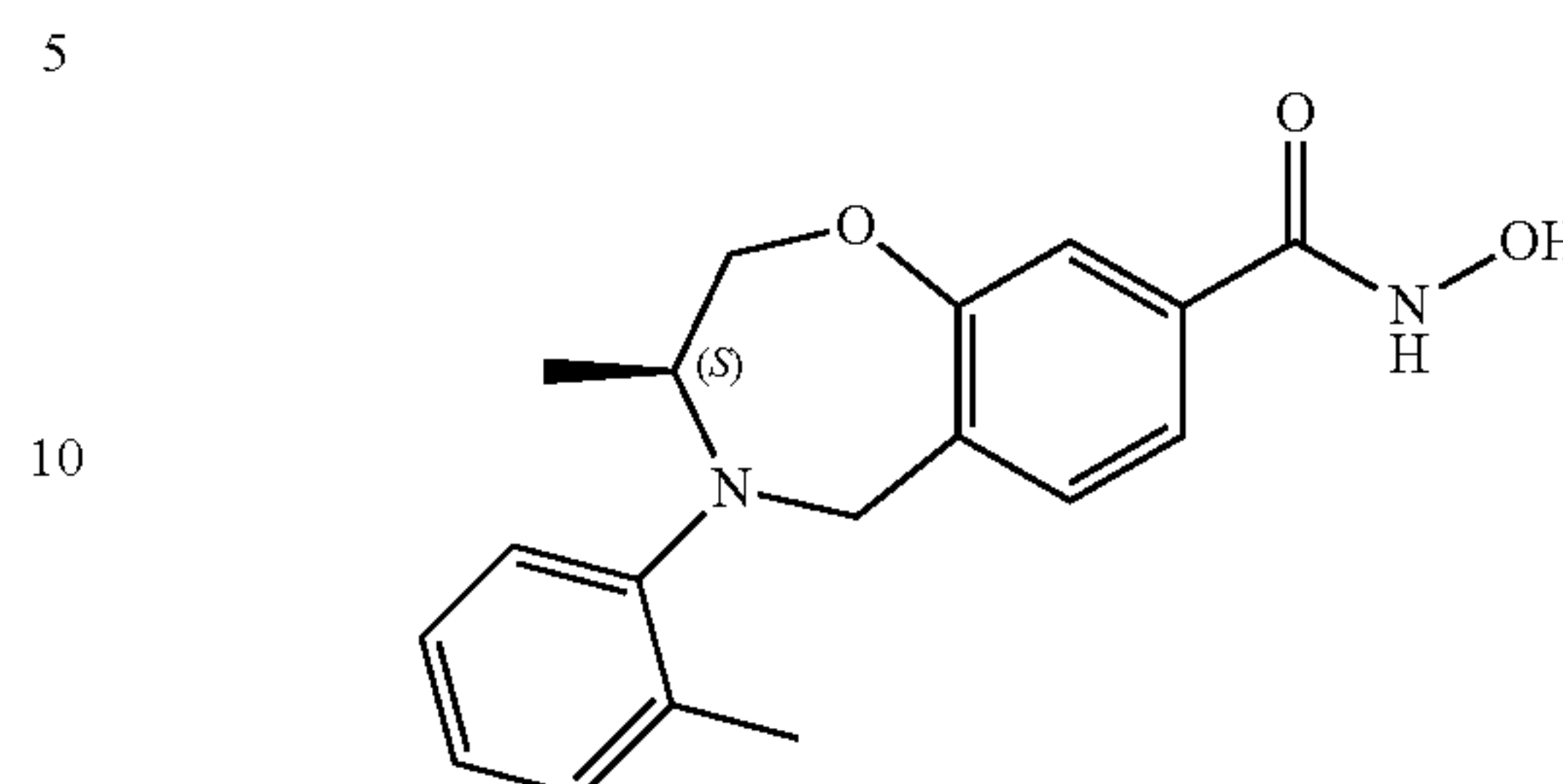
Step-1: Methyl (S)-3-methyl-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (200 mg, 0.90 mmol, 1 equiv) in toluene (3 mL), 1-bromo-2-methylbenzene (462 mg, 2.70 mmol, 3 equiv), Cs<sub>2</sub>CO<sub>3</sub> (887 mg, 2.70 mmol, 3 equiv), BINAP (225 mg, 0.36 mmol, 0.4 equiv) and Pd(OAc)<sub>2</sub> (41 mg, 0.18 mmol, 0.2 equiv). The resulting solution was stirred for 20 h at 110° C. in an oil bath. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with H<sub>2</sub>O (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with H<sub>2</sub>O (2×10 mL) and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:5) to afford the title compound as a yellow oil (30 mg, 11% yield). MS: (ES, m/z): 312[M+H]<sup>+</sup>.

## 128

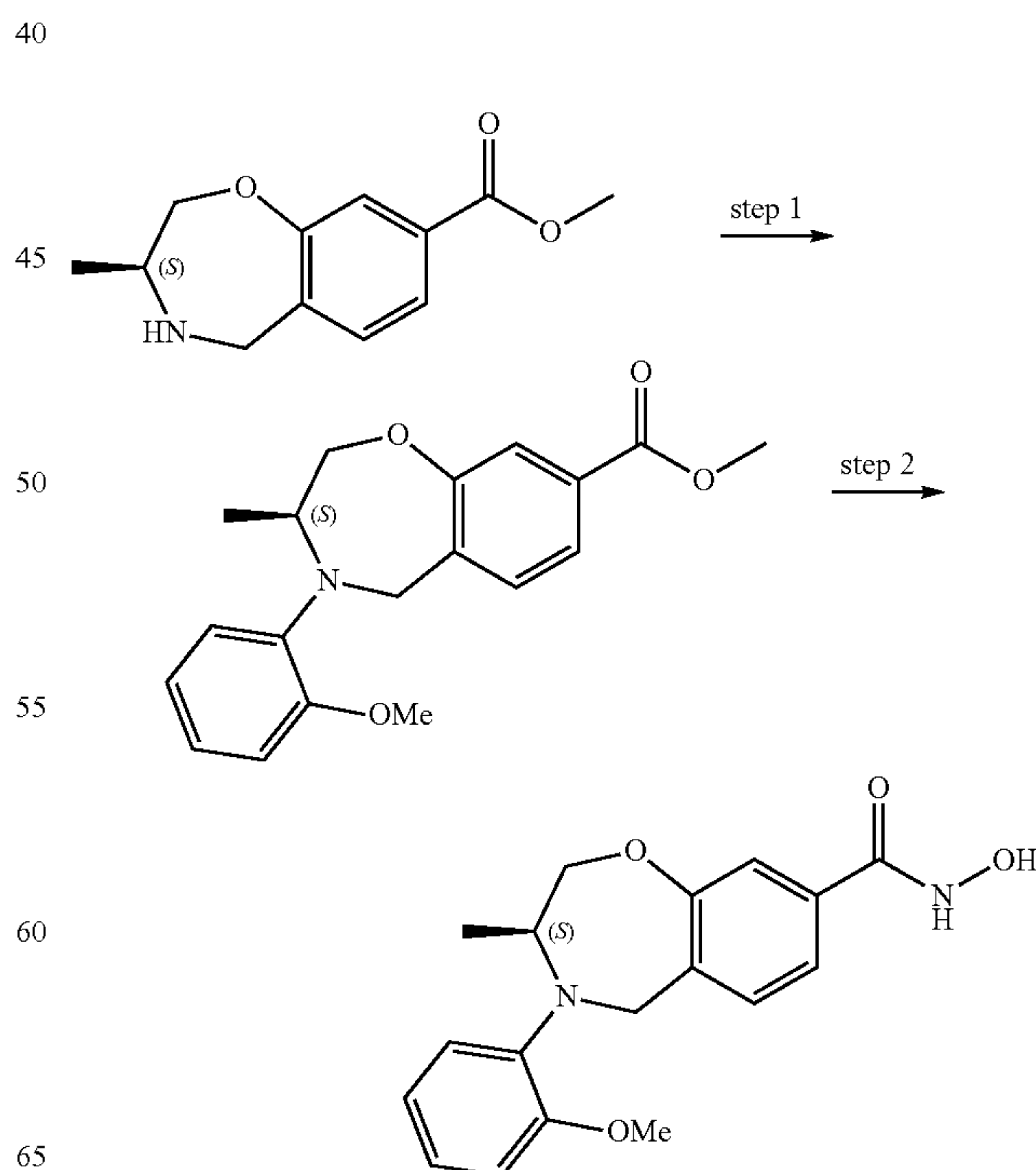
Step-2: (S)—N-hydroxy-3-methyl-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed a solution of methyl (S)-3-methyl-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (30 mg, 0.10 mmol, 1 equiv) in THF/MeOH (4:1, 3 mL). This was followed by the addition of NH<sub>2</sub>OH (50% in water, 0.19 mL, 30 equiv) and aq. 1N NaOH (0.19 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 15% B to 60% B in 7 min; Detector: UV 254, 220 nm) to afford the title compound as a white solid (8.2 mg, 24% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 7.44-7.33 (m, 2H), 7.30 (m, 1H), 7.29-7.12 (m, 3H), 6.98-6.96 (m, 1H), 4.46-4.39 (m, 2H), 4.31-4.16 (m, 1H), 4.08-4.04 (m, 1H), 3.70 (s, 1H), 2.18 (s, 3H), 1.04-1.02 (d, J=8.0 Hz, 3H). MS: (ES, m/z): 313 [M+H]<sup>+</sup>.

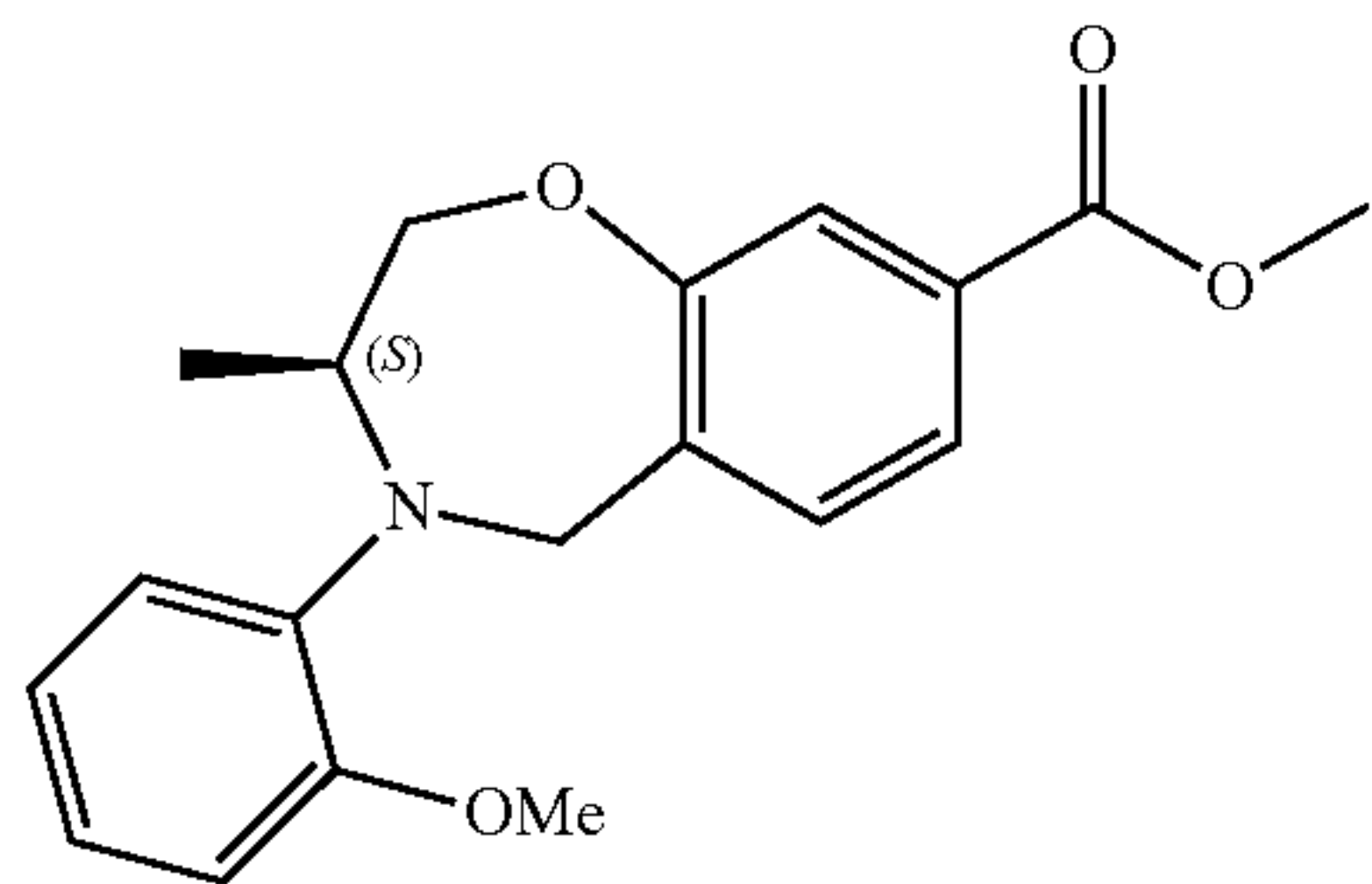
## Example 42

Preparation of (S)—N-hydroxy-4-(2-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



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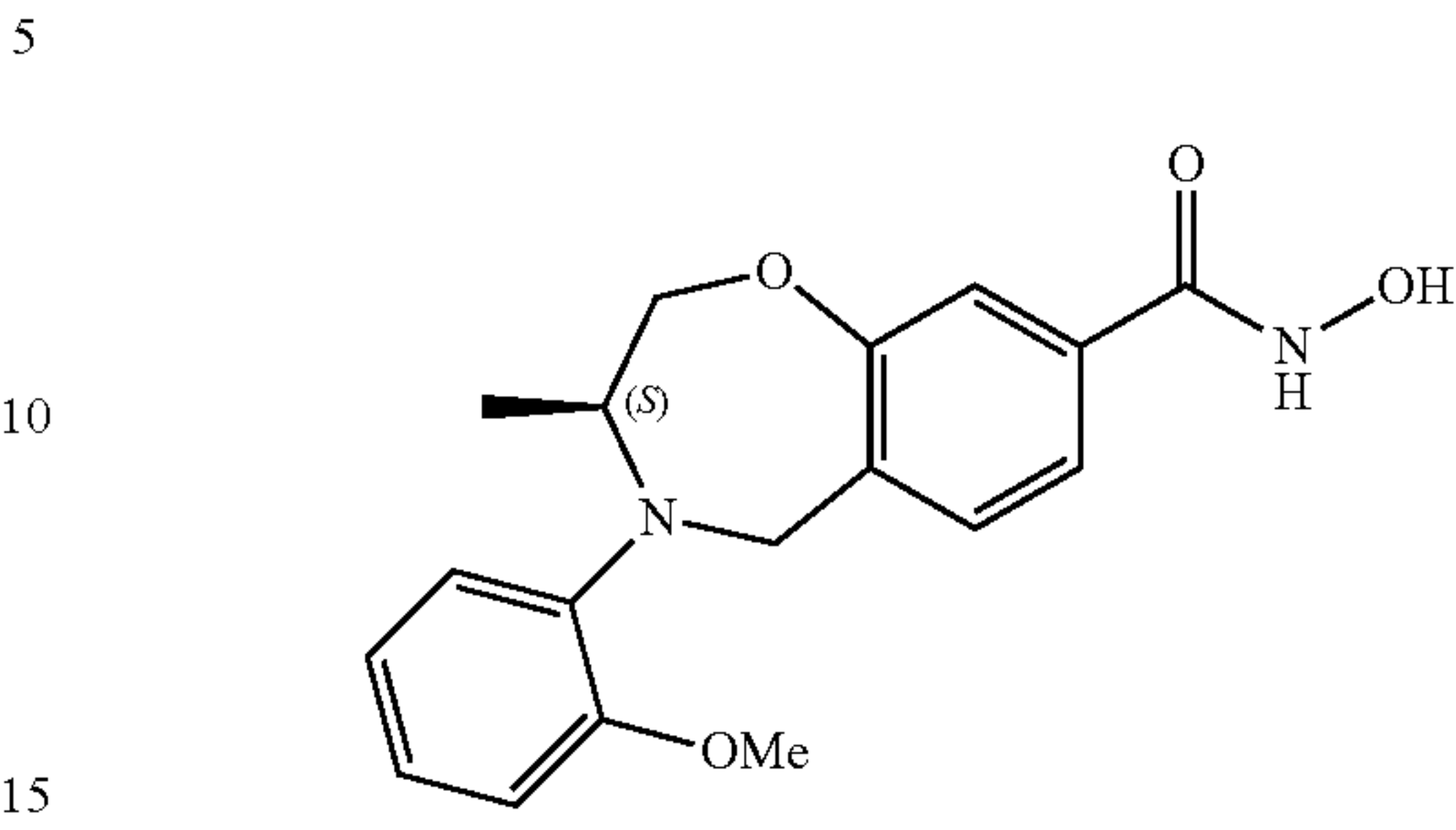
Step-1: Methyl (S)-4-(2-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 100-mL round-bottom flask, was placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (220 mg, 0.99 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL), (2-methoxyphenyl)boronic acid (452 mg, 2.97 mmol, 3 equiv), Et<sub>3</sub>N (300 mg, 2.97 mmol, 3 equiv) and Cu(OAc)<sub>2</sub> (182 mg, 1.00 mmol, 1 equiv). To the above oxygen gas was introduced in. The resulting solution was stirred for 27 h at room temperature and then washed with H<sub>2</sub>O (3×10 mL). The organic layers was concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a solid (50 mg, 15% yield)  
MS: (ES, m/z): 328 [M+H]<sup>+</sup>.

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Step-2: (S)—N-Hydroxy-4-(2-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



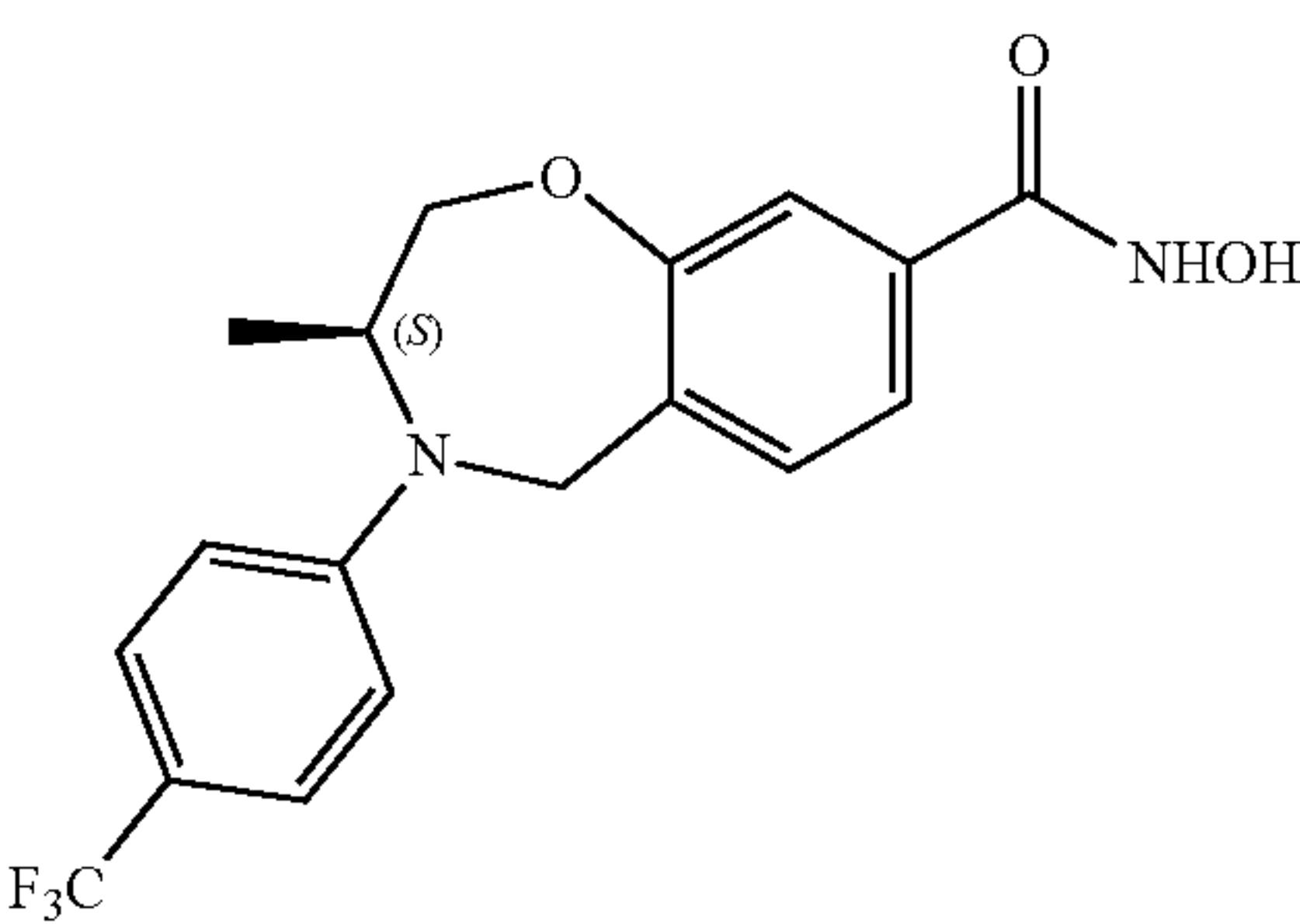
Into a 8-mL vial, was placed a solution of methyl (S)-4-(2-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (50 mg, 0.15 mmol, 1 equiv) in THF/MeOH (4:1, 1.5 mL). This was followed by the addition of NH<sub>2</sub>OH (50% in water, 0.30 mL, 30 equiv). To this was added aq. 1N NaOH (0.30 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 119×150 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 5% B to 60% B in 8 min; Detector: UV 254, 220 nm) to afford the title compound as a yellow solid (3.9 mg, 7% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.24 (br s, 1H), 7.40-7.38 (m, 1H), 7.33-7.31 (m, 1H), 7.26-7.20 (m, 1H), 7.15-6.78 (m, 4H), 4.74-4.70 (d, J=16.0 Hz, 1H), 4.35-4.31 (m, 2H), 4.16-4.13 (m, 2H), 3.87 (s, 3H), 1.14-1.13 (d, J=4.0 Hz, 3H). MS: (ES, m/z): 329 [M+H]<sup>+</sup>.

TABLE 20

The following compounds were prepared according to the method of Example 42.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 11.09 (s, 1H), 8.98 (s, 1H), 7.46-7.44 (m, 1H), 7.33-317 7.31 (m, 1H), 7.09 (s, 1H), 6.92-6.87 (m, 2H), 6.63-[M + H] <sup>+</sup> 6.60 (m, 2H), 5.00-4.96 (m, 1H), 4.36-4.26 (m, 2H), 4.21-4.15 (m, 2H), 1.22-1.17 (m 3H)	
	(ES, m/z): 11.08 (s, 1H), 8.98 (s, 1H), 7.50-7.48 (d, J = 8 Hz, 317 1H), 7.33-7.30 (m, 1H), 7.09-7.03 (m, 2H), 6.49-6.46 [M + H] <sup>+</sup> (m, 1H), 6.43-6.38 (d, J = 8 Hz, 1H), 6.33-6.28 (m, 1H), 5.03-4.99 (d, J = 8 Hz, 1H), 4.40-4.27 (m, 2H), 4.26-4.18 (m, 2H), 1.22-1.18 (m, 3H)	

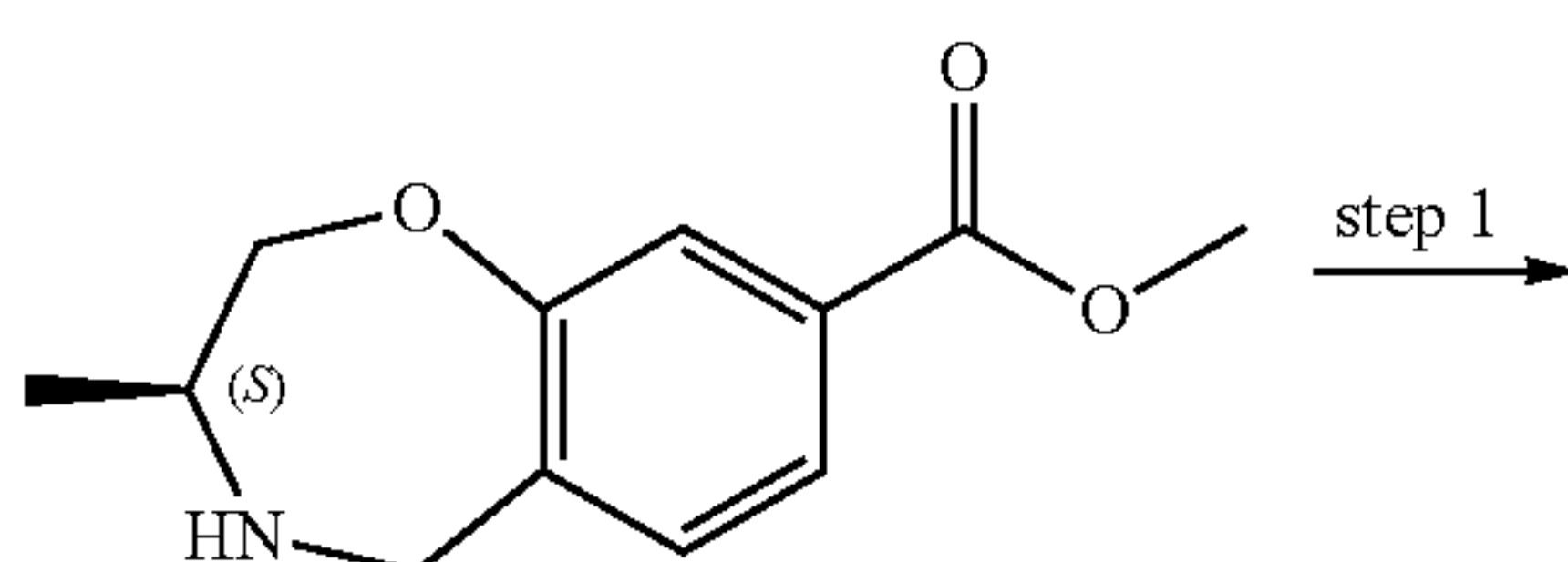


TABLE 20-continued

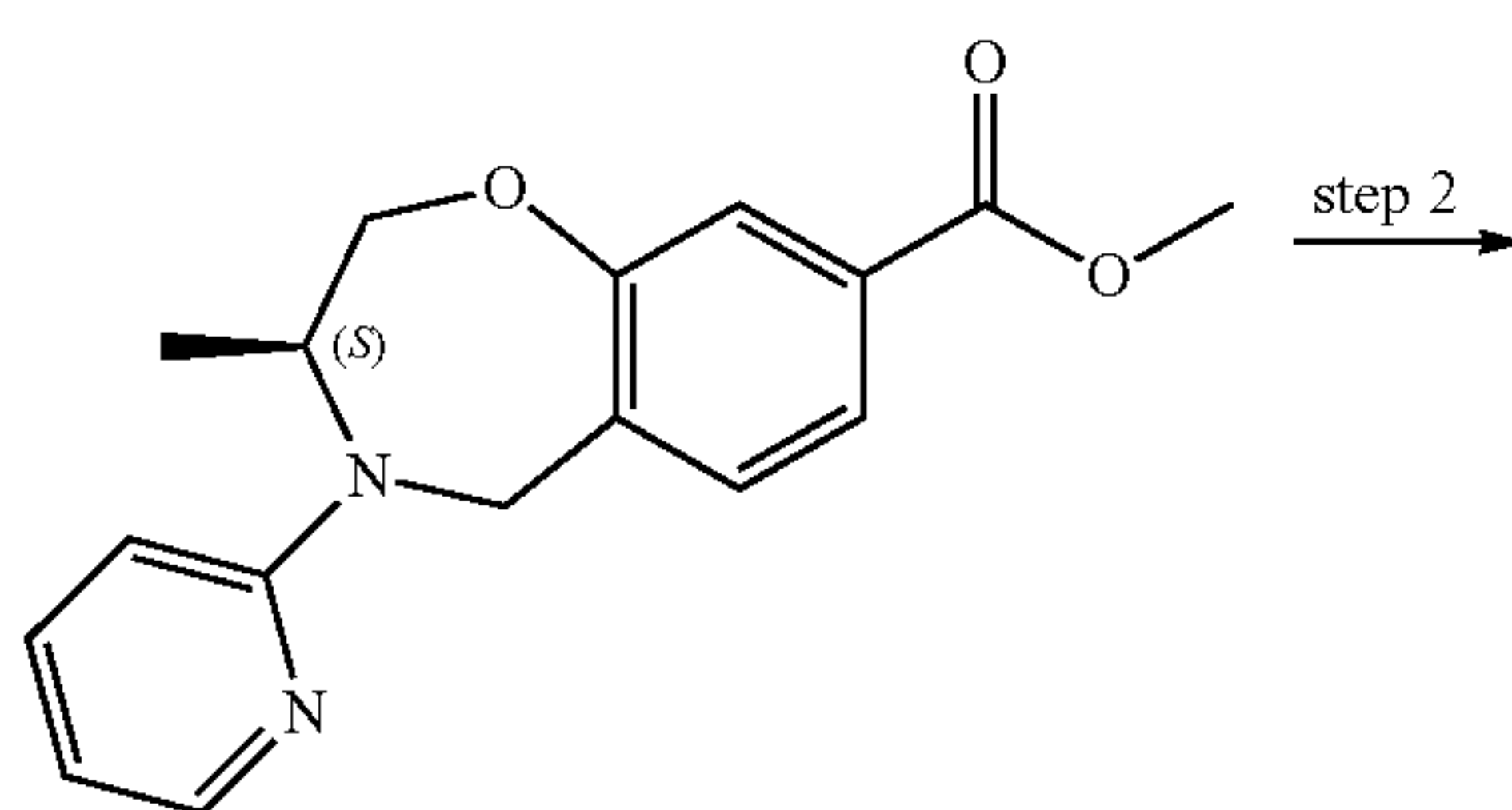
The following compounds were prepared according to the method of Example 42.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 367 [M + H] <sup>+</sup>	11.06 (s, 1H), 8.99 (s, 1H), 7.52-7.50 (d, J = 7.8 Hz, 1H), 7.40-7.33 (m, 3H), 7.12-7.11 (d, J = 1.5 Hz, 1H), 6.81-6.78 (d, J = 9 Hz, 2H), 5.12-5.06 (d, J = 17.4 Hz, 1H), 4.47-4.37 (m, 3H), 4.35-4.22 (m, 1H), 1.22-1.20 (d, J = 6 Hz, 3H)

## Example 43

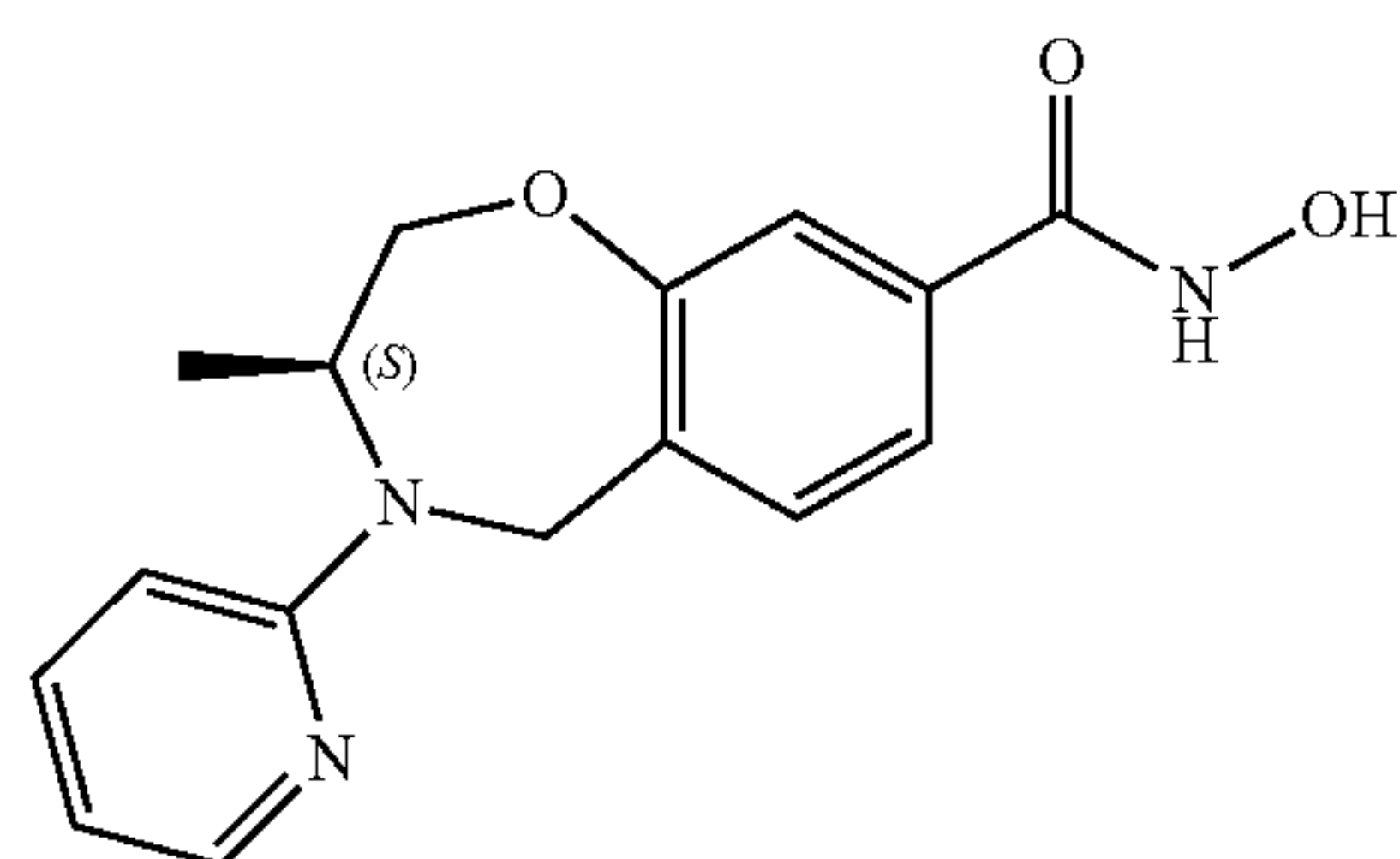
Preparation of (S)—N-hydroxy-3-methyl-4-(pyridin-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



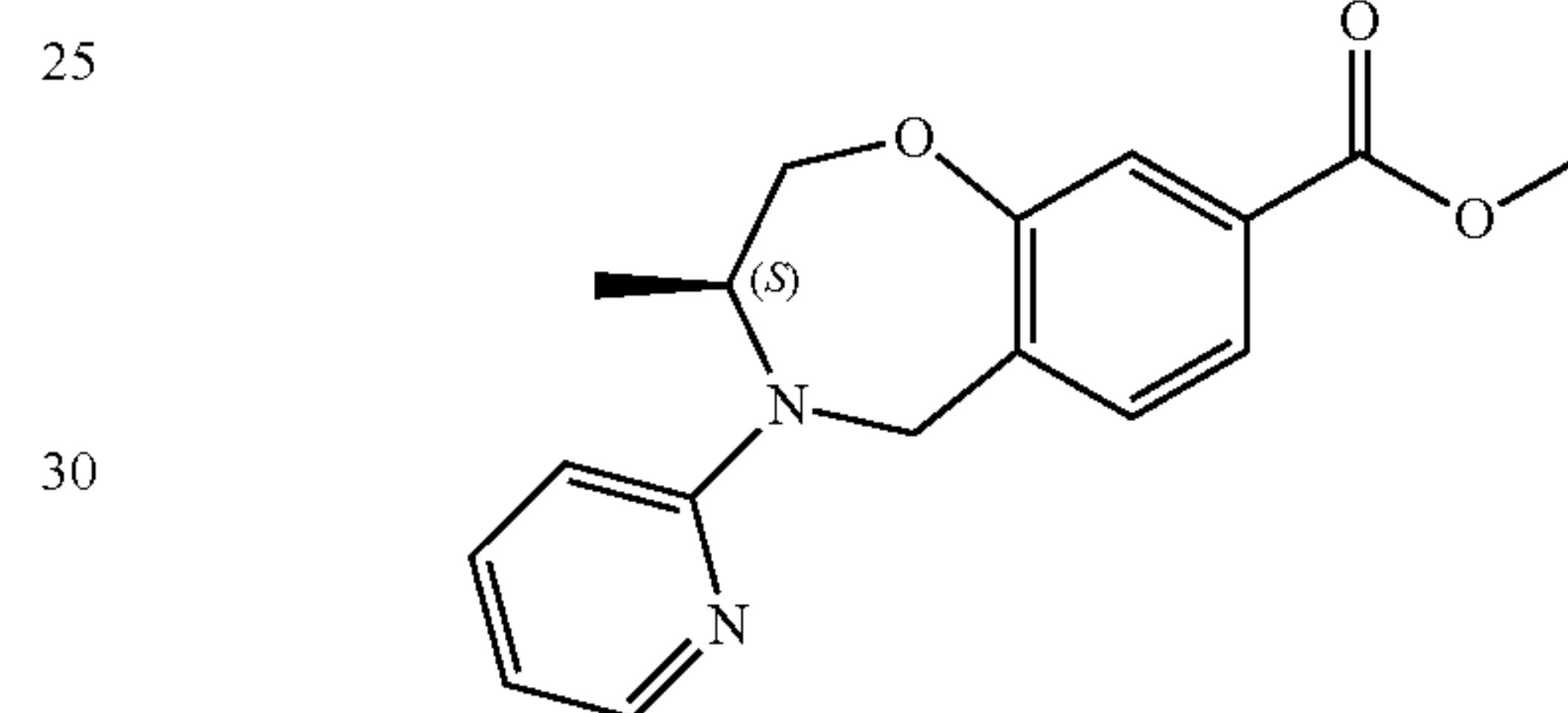
step 1



step 2

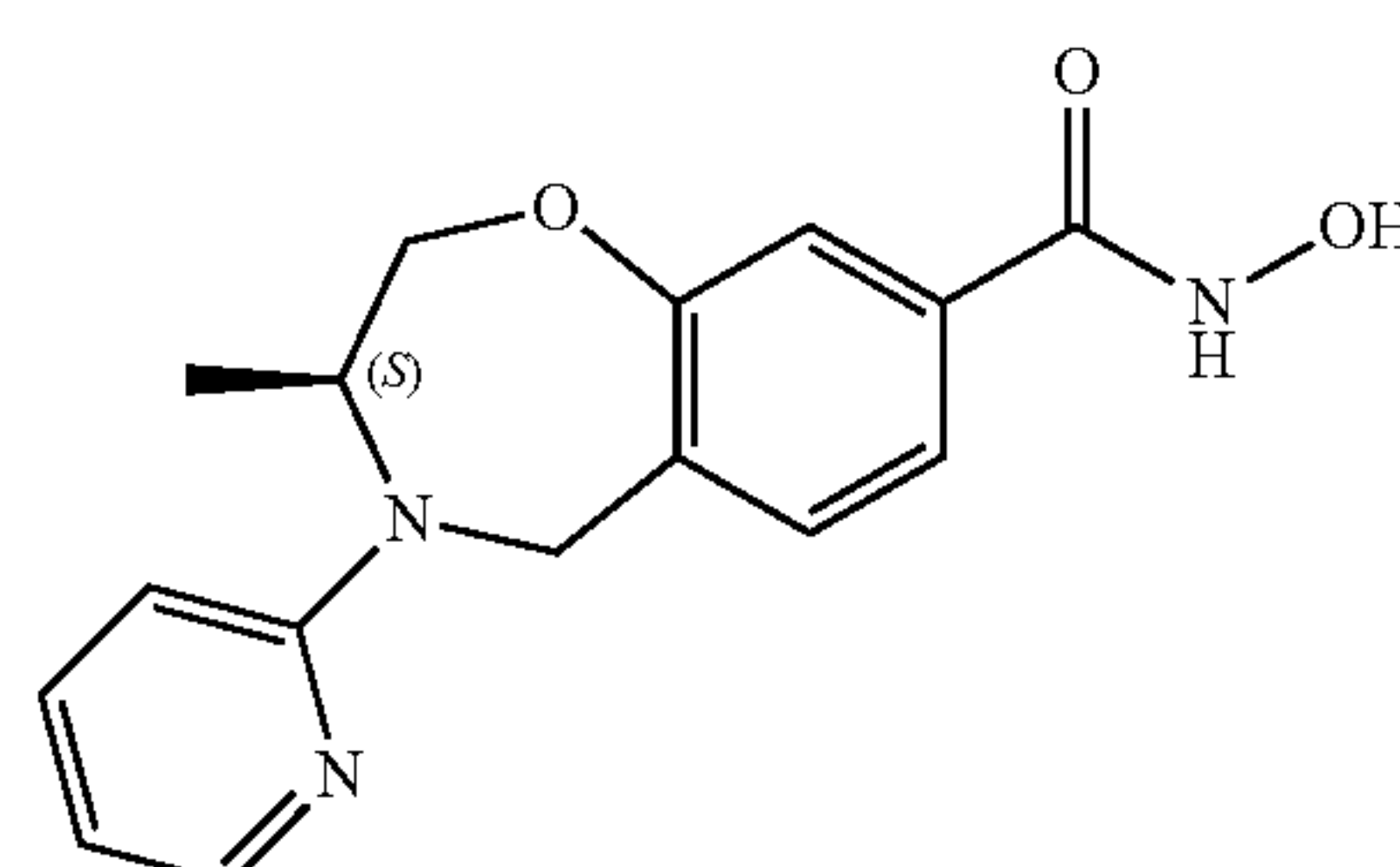


Step-1: Methyl (S)-3-methyl-4-(pyridin-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, were placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (200 mg, 0.90 mmol, 1 equiv) in toluene (3 mL), 2-bromopyridine (529 mg, 3.35 mmol, 3 equiv), RuPhos (169 mg, 0.36 mmol, 0.4 equiv), t-BuONa (213 mg, 2.22 mmol, 3 equiv) and Pd<sub>2</sub>(dba)<sub>3</sub>.CHCl<sub>3</sub> (187 mg, 0.18 mmol, 0.2 equiv). The resulting mixture was stirred for 18 h at 120° C. in an oil bath. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was dissolved in EtOAc (20 mL), washed with H<sub>2</sub>O (2×20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a light brown oil (110 mg, 41% yield). MS: (ES, m/z): 299 [M+H]<sup>+</sup>.

Step-2: (S)—N-Hydroxy-3-methyl-4-(pyridin-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



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Into a 8-mL vial, was placed a solution of methyl (S)-3-methyl-4-(pyridin-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.34 mmol, 1 equiv) in THF/MeOH (4:2, 1.5 mL). This was followed by the addition of aq. 1N NaOH (0.67 mL, 2 equiv) and NH<sub>2</sub>OH (50% in water, 0.61 mL, 30 equiv) simultaneously. The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×100 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 5% B to 50% B in 6 min; Detector: UV 254, 220 nm) to afford the title compound as a light brown solid (13.3 mg, 13% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.15 (br s, 1H), 8.10-8.00 (m, 1H), 7.90-7.71 (m, 1H), 7.63-7.50 (m, 1H), 7.45-7.35 (m, 1H), 7.23-7.10 (m, 1H), 7.09-6.70 (m, 2H), 5.29-5.10 (m, 1H), 4.95-4.74 (m, 2H), 4.59-4.23 (m, 2H), 1.30-1.12 (m, 3H). MS: (ES, m/z): 300 [M+H]<sup>+</sup>.

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-continued

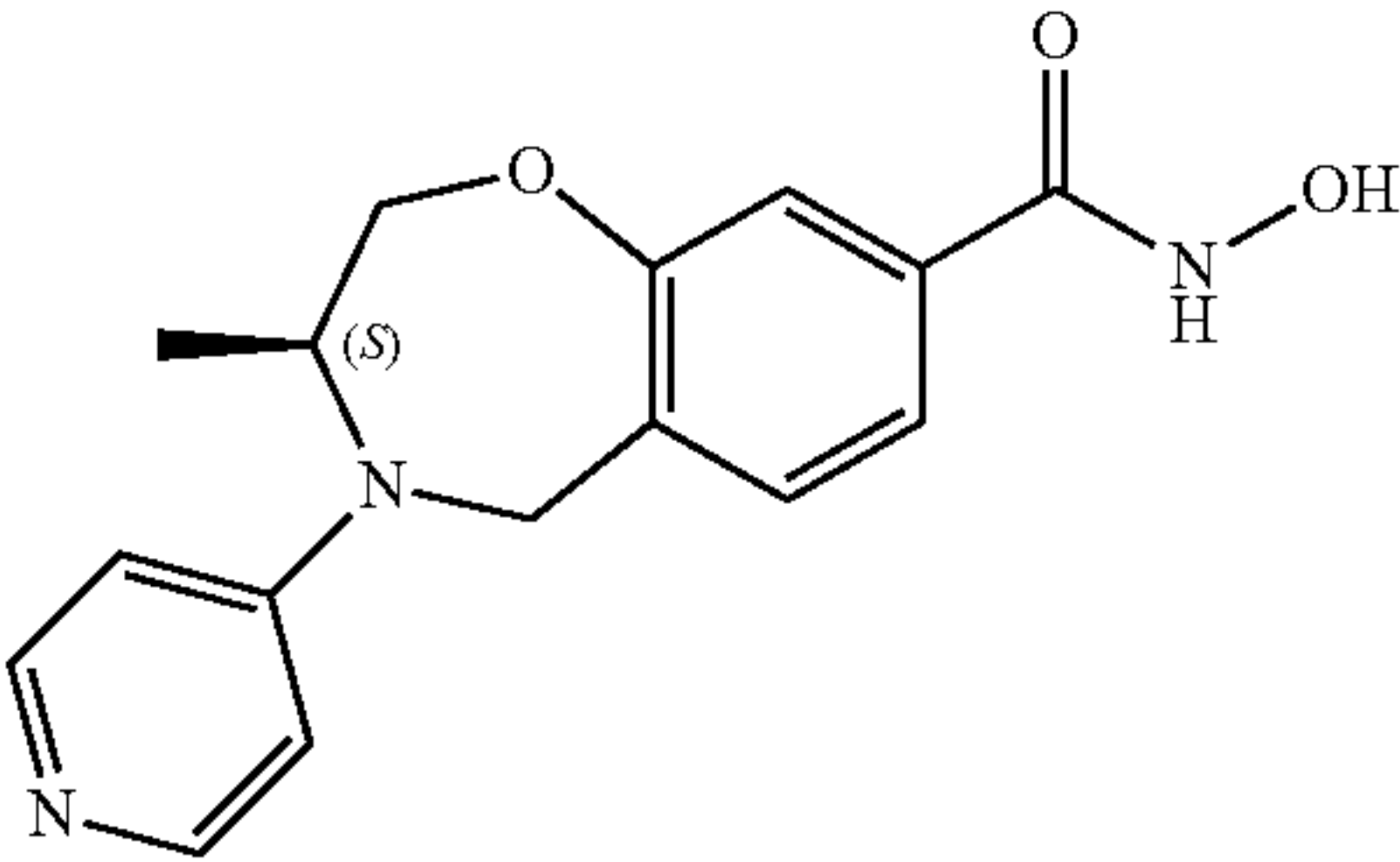
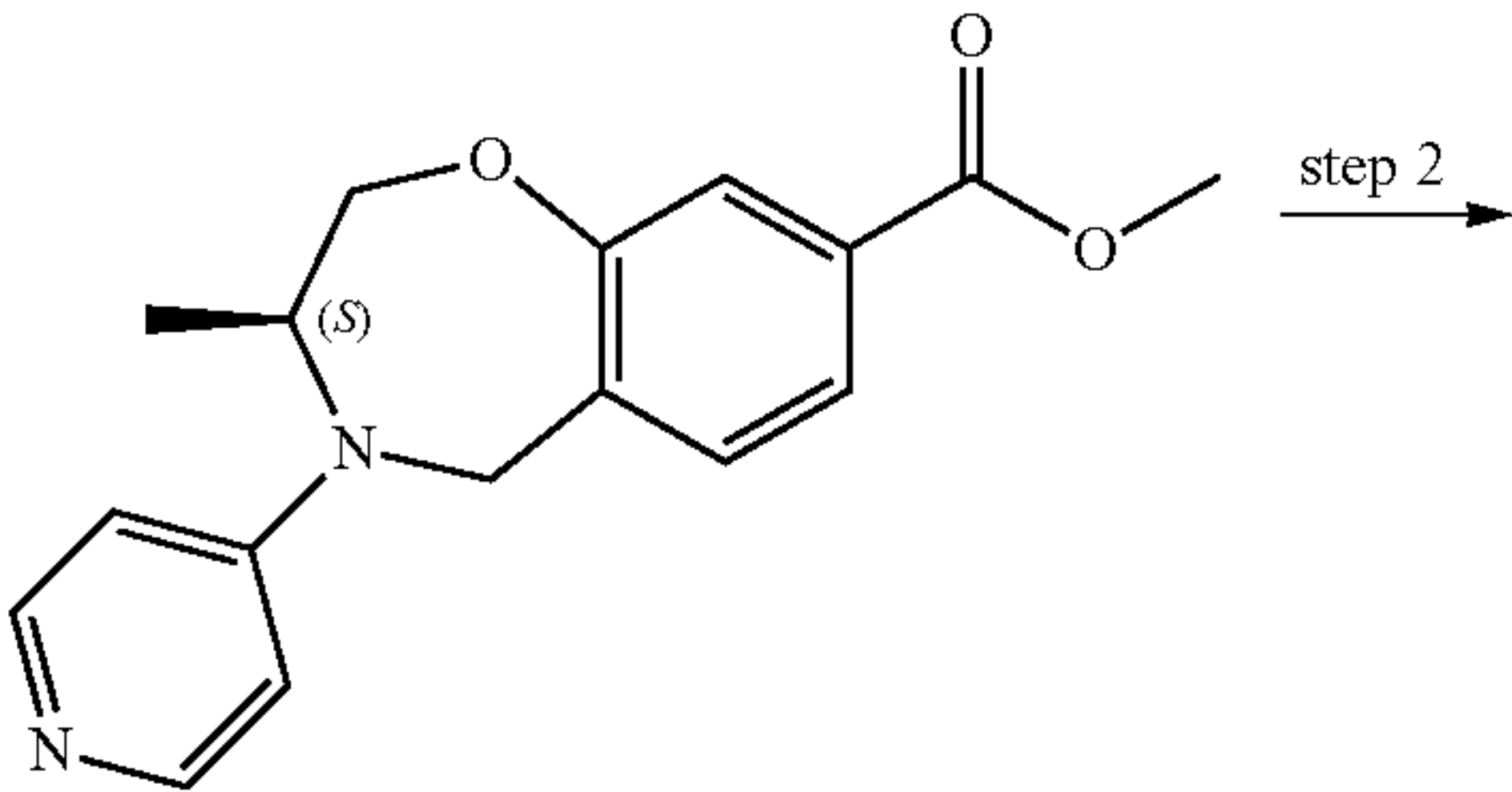
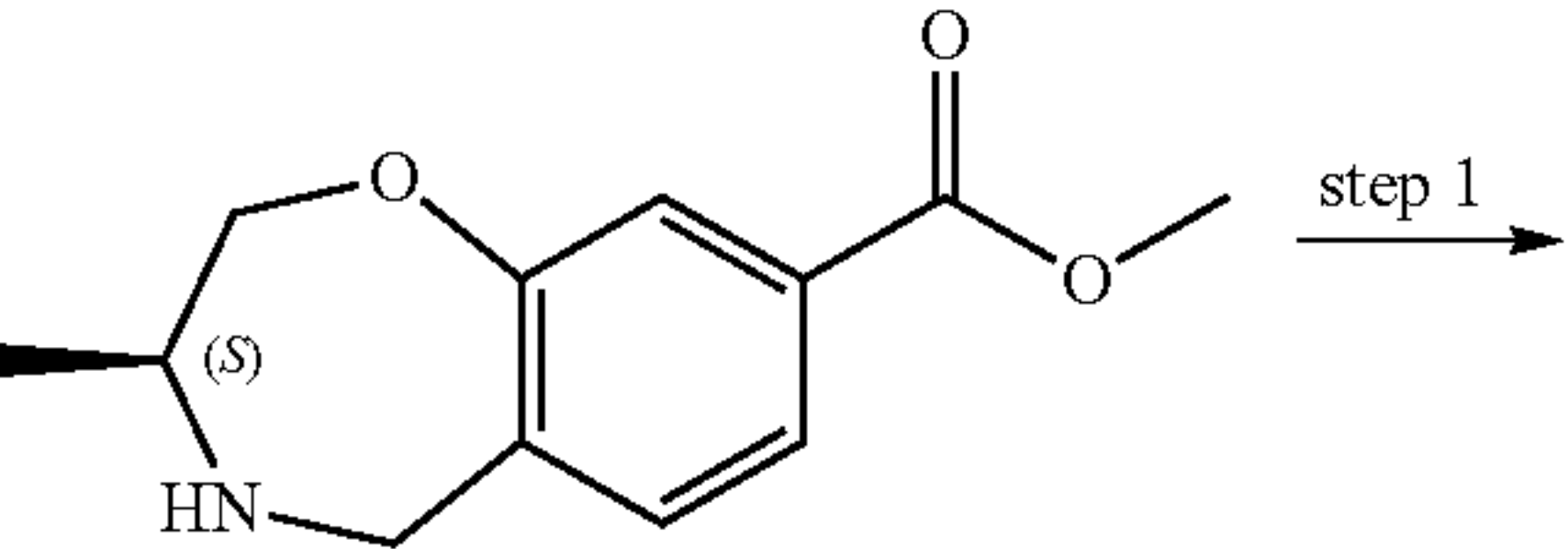


TABLE 21

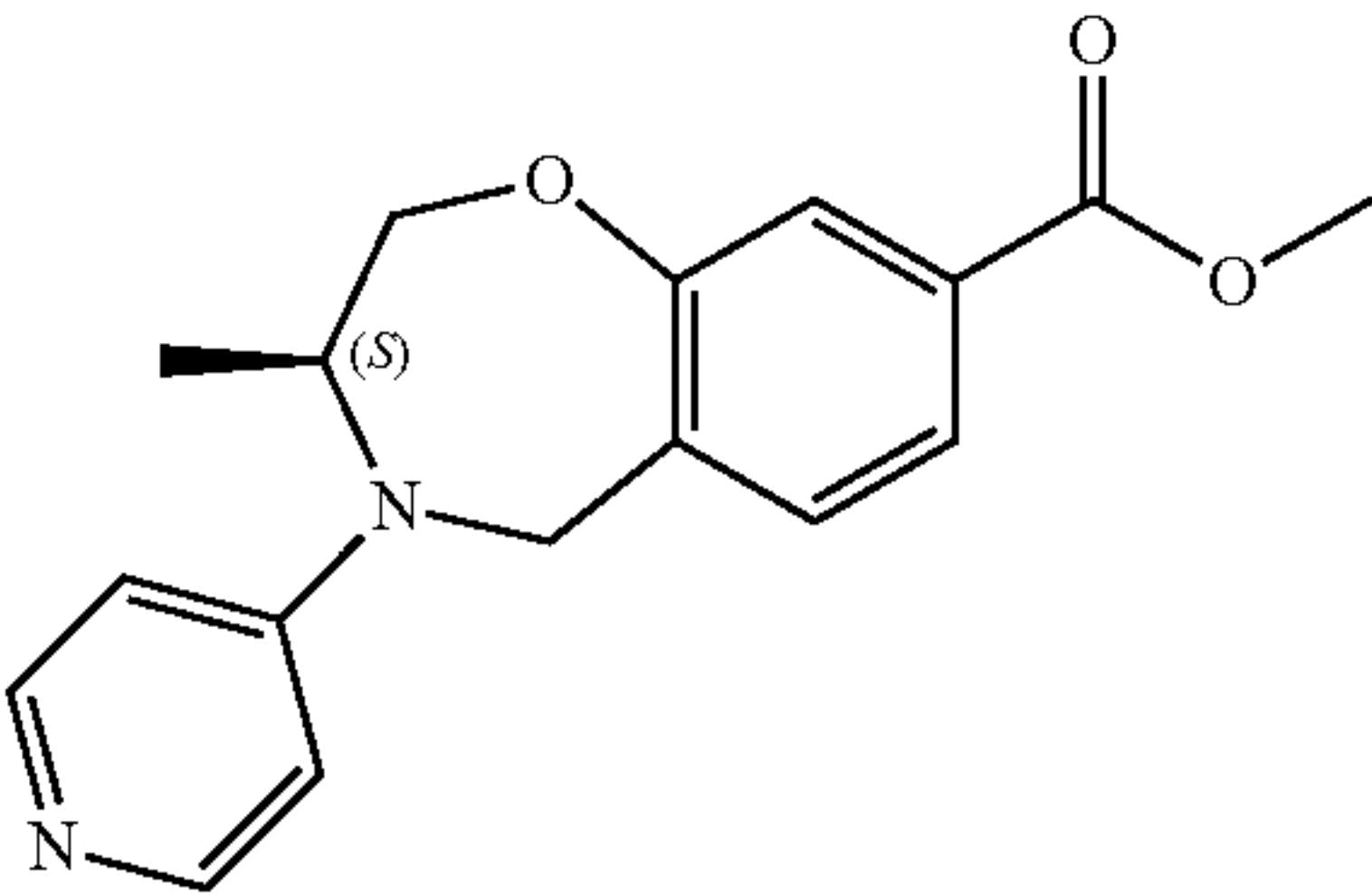
The following compound was prepared according to the method of Example 43.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 11.18 (m, 1H), 8.24-8.23 (d, J = 1.4 Hz, 1H), 8.05-8.04 (d, J = 2.6 Hz, 1H), 7.88-7.85 (m, 1H), 7.76-7.73 (m, 1H), 7.59-7.57 (d, J = 4.0 Hz, 1H), 7.45-7.33 (m, 1H), 7.16-7.15 (d, J = 0.8 Hz, 1H), 5.22-5.18 (d, J = 8.8 Hz, 1H), 4.65-4.61 (d, J = 9.0 Hz, 1H), 4.52-4.47 (m, 2H), 4.32-4.25 (m, 1H), 1.25-1.23 (d, J = 2.6 Hz, 3H)	

Example 44

Preparation of (S)—N-hydroxy-3-methyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Step-1: Methyl (S)-3-methyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

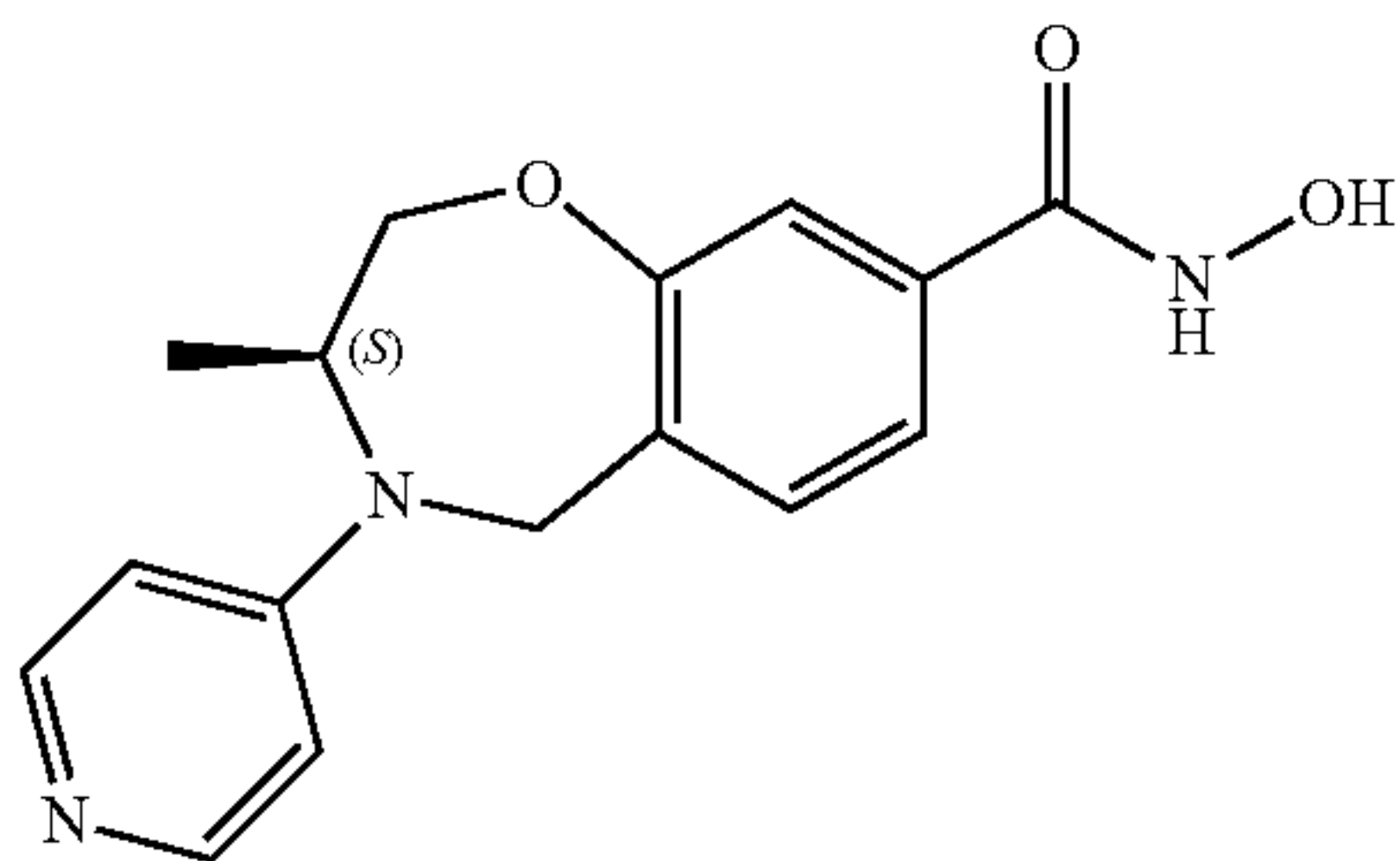


Into a 25-mL sealed tube, were placed methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (150 mg, 0.45 mmol, 1 equiv) in toluene (5 mL), 4-bromopyridine hydrochloride (174 mg, 0.89 mmol, 2 equiv), RuPhos-Pd-G2 (35 mg, 0.05 mmol, 0.1 equiv), RuPhos (21 mg, 0.04 mmol, 0.1 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (438 mg, 1.34 mmol, 3 equiv). The resulting solution was stirred for 18 h at 100° C. in an oil bath. The resulting mixture was concentrated under vacuum. The residue was dissolved in EtOAc (50 mL), washed with H<sub>2</sub>O (3×30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:12) to afford the title compound as a yellow oil (74.6 mg, 56% yield). MS: (ES, m/z): 299 [M+H]<sup>+</sup>.



**135**

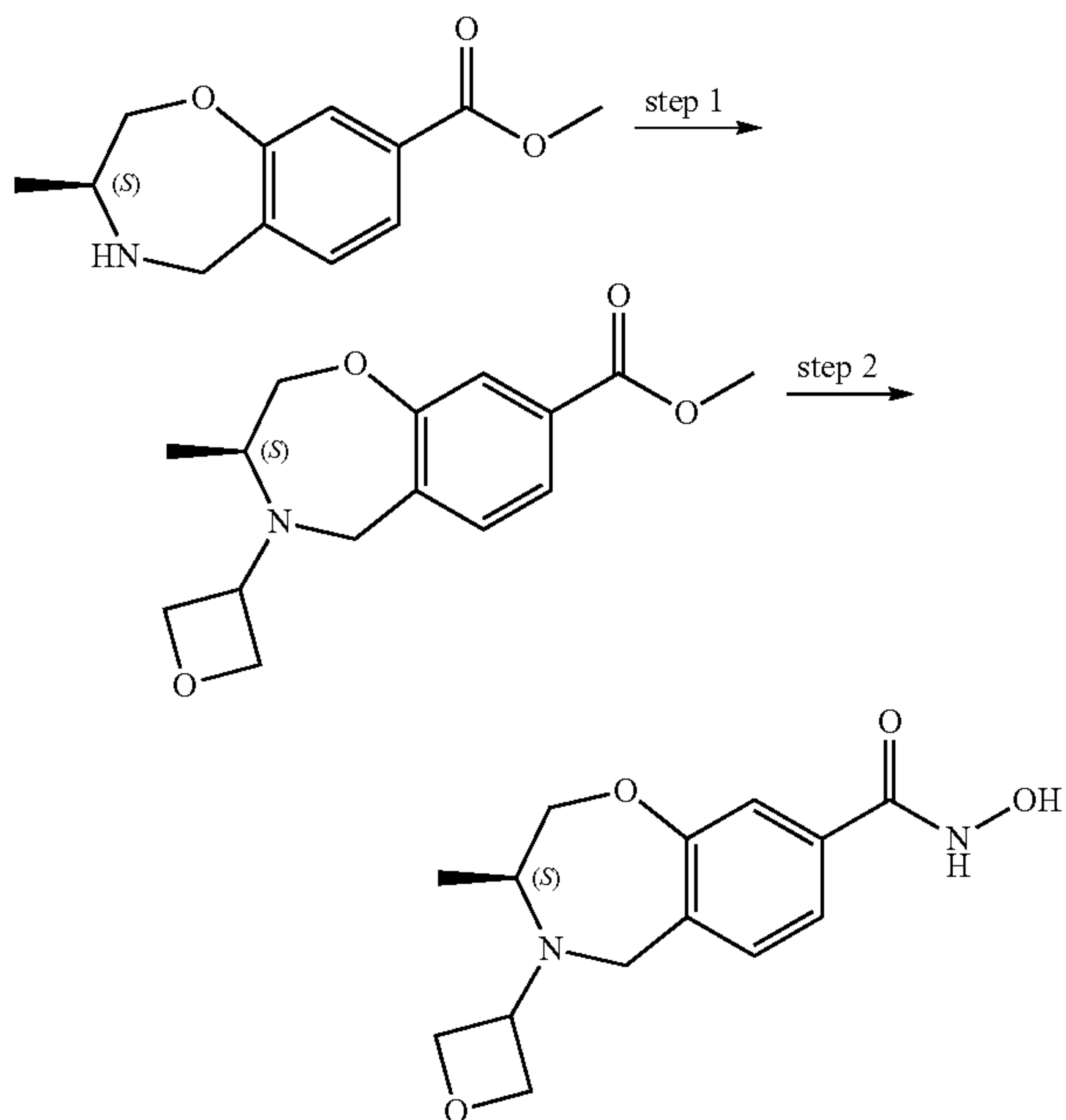
Step-2: (S)—N-Hydroxy-3-methyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



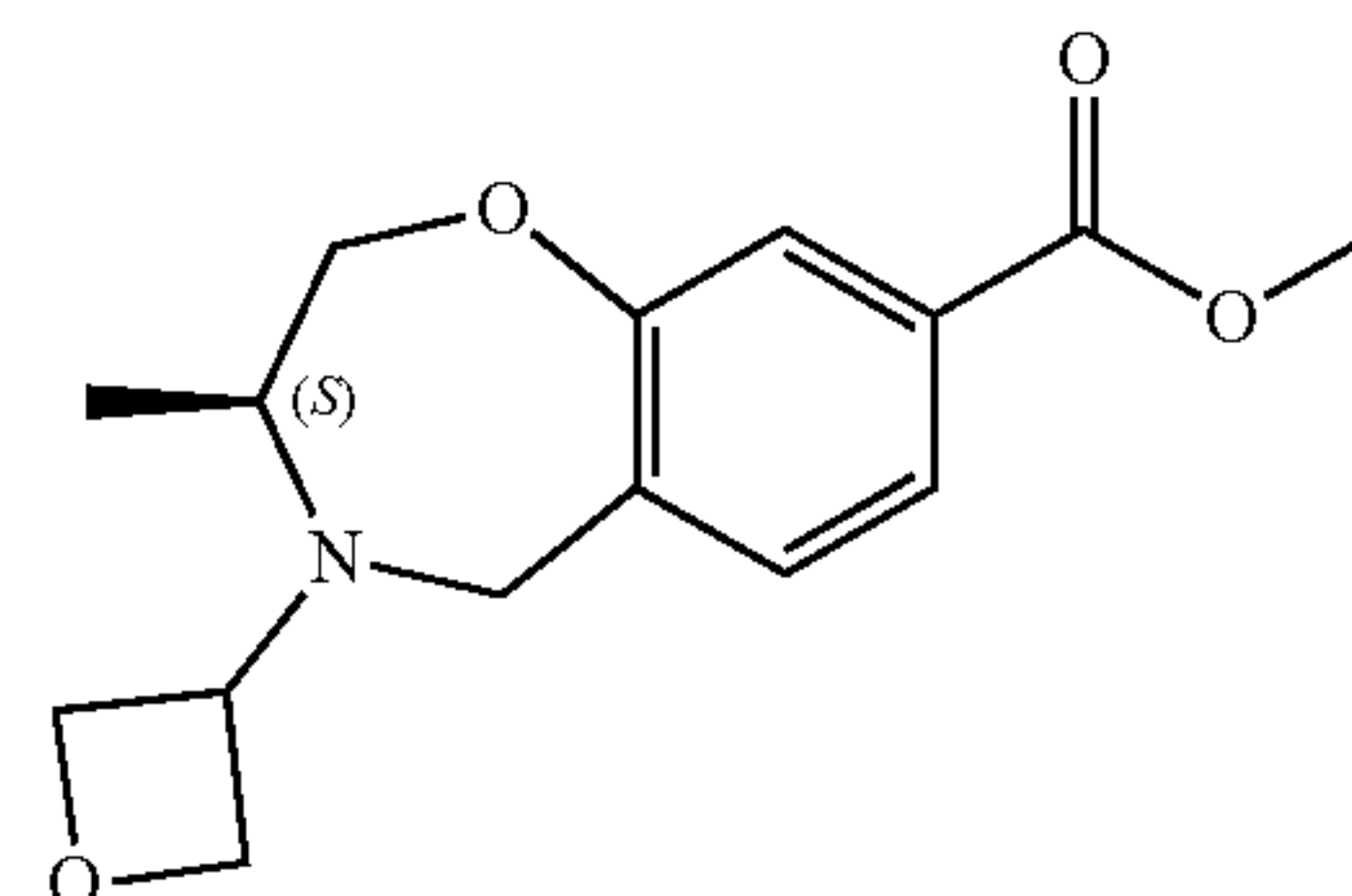
Into a 8-mL vial, was placed a solution of methyl (S)-3-methyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (78 mg, 0.26 mmol, 1 equiv) in THF/MeOH (4:1, 3 mL). This was followed by  $\text{NH}_2\text{OH}$  (50% in water, 0.52 mL, 30 equiv) and aq. 1N NaOH (0.52 mL, 2 equiv) dropwise with stirring simultaneously. The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5  $\mu\text{m}$ , 119 $\times$ 150 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 20 mL/min; Gradient: 3% B to 12% B in 8 min; Detector: UV 254, 220 nm) to afford the title compound as an off-white solid (35.7 mg, 46% yield).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.13-11.09 (br s, 1H), 8.04-8.02 (d,  $J=2.8$  Hz, 2H), 7.51-7.49 (d,  $J=4.0$  Hz, 1H), 7.33-7.30 (m, 1H), 7.10-7.09 (d,  $J=0.8$  Hz, 1H), 6.65-6.61 (m, 2H), 5.06-5.01 (m, 1H), 4.47-4.31 (m, 3H), 4.25-4.21 (m, 1H), 1.16-1.15 (d,  $J=2.0$  Hz, 3H). MS: (ES,  $m/z$ ): 300  $[\text{M}+\text{H}]^+$ .

## Example 45

Preparation of (S)—N-hydroxy-3-methyl-4-(oxetan-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

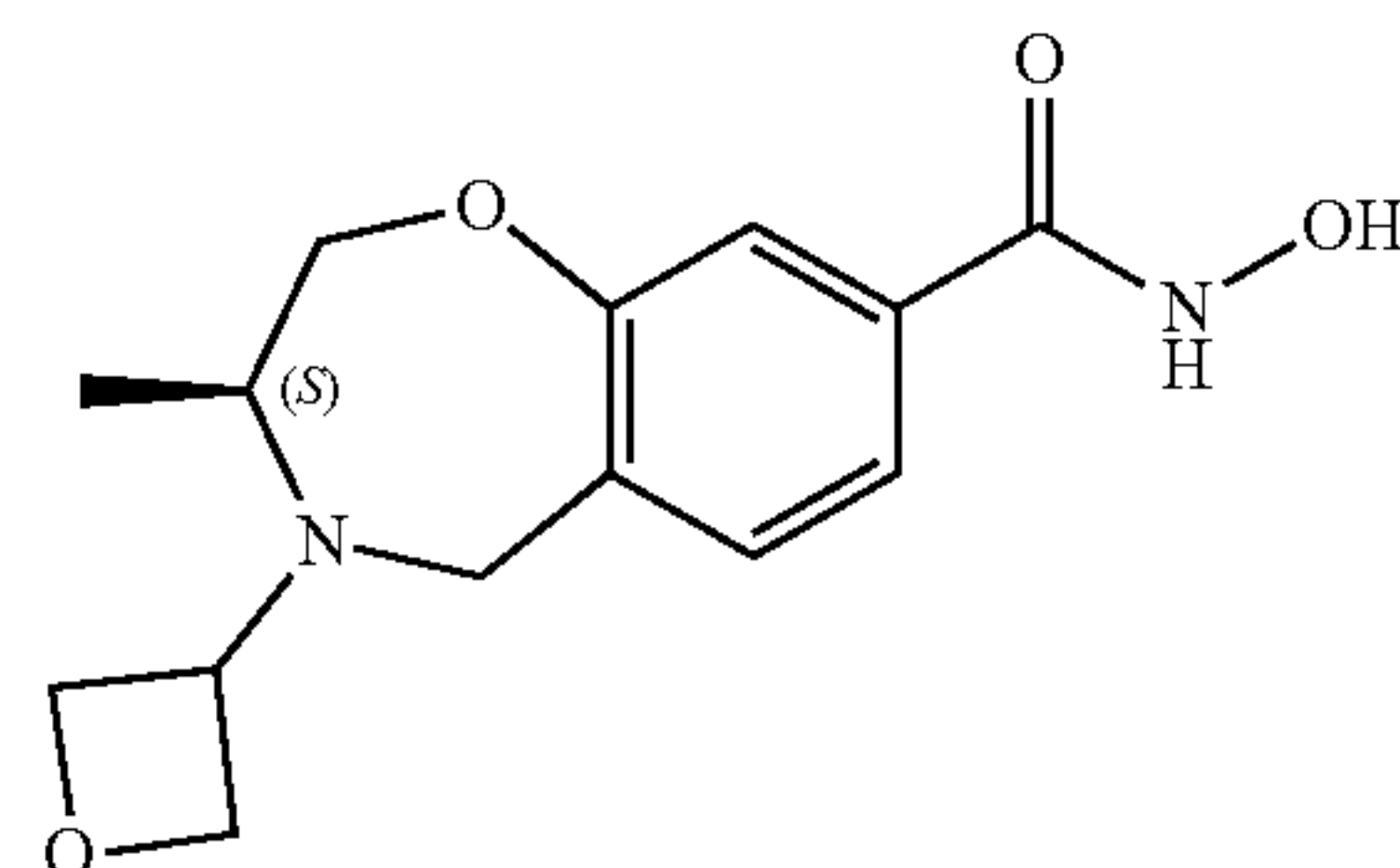
**136**

Step-1: Methyl (S)-3-methyl-4-(oxetan-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8 mL vial were added methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate hydrochloride (50 mg, 0.194 mmol, 1 equiv) and  $\text{Et}_3\text{N}$  (0.027 mL, 0.194 mmol, 1 equiv) and 1,2-dichloroethane (5 mL). This solution was stirred at room temperature for 15 minutes. Next, oxetan-3-one (16.8 mg, 0.233 mmol, 1.2 equiv), acetic acid (0.011 mL, 0.194 mmol, 1 equiv), and  $\text{NaBH}(\text{OAc})_3$  (103 mg, 0.485 mmol, 2.5 equiv) were added. The resulting solution was allowed to stir at 50° C. for 16 hours. The reaction was washed with  $\text{H}_2\text{O}$  (2 $\times$ 5 mL). The organic layer was separated, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to afford the title compound as a white solid (65 mg) that was used without further purification. MS: (ES,  $m/z$ ): 278  $[\text{M}+\text{H}]^+$ .

Step-2: (S)—N-Hydroxy-3-methyl-4-(oxetan-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

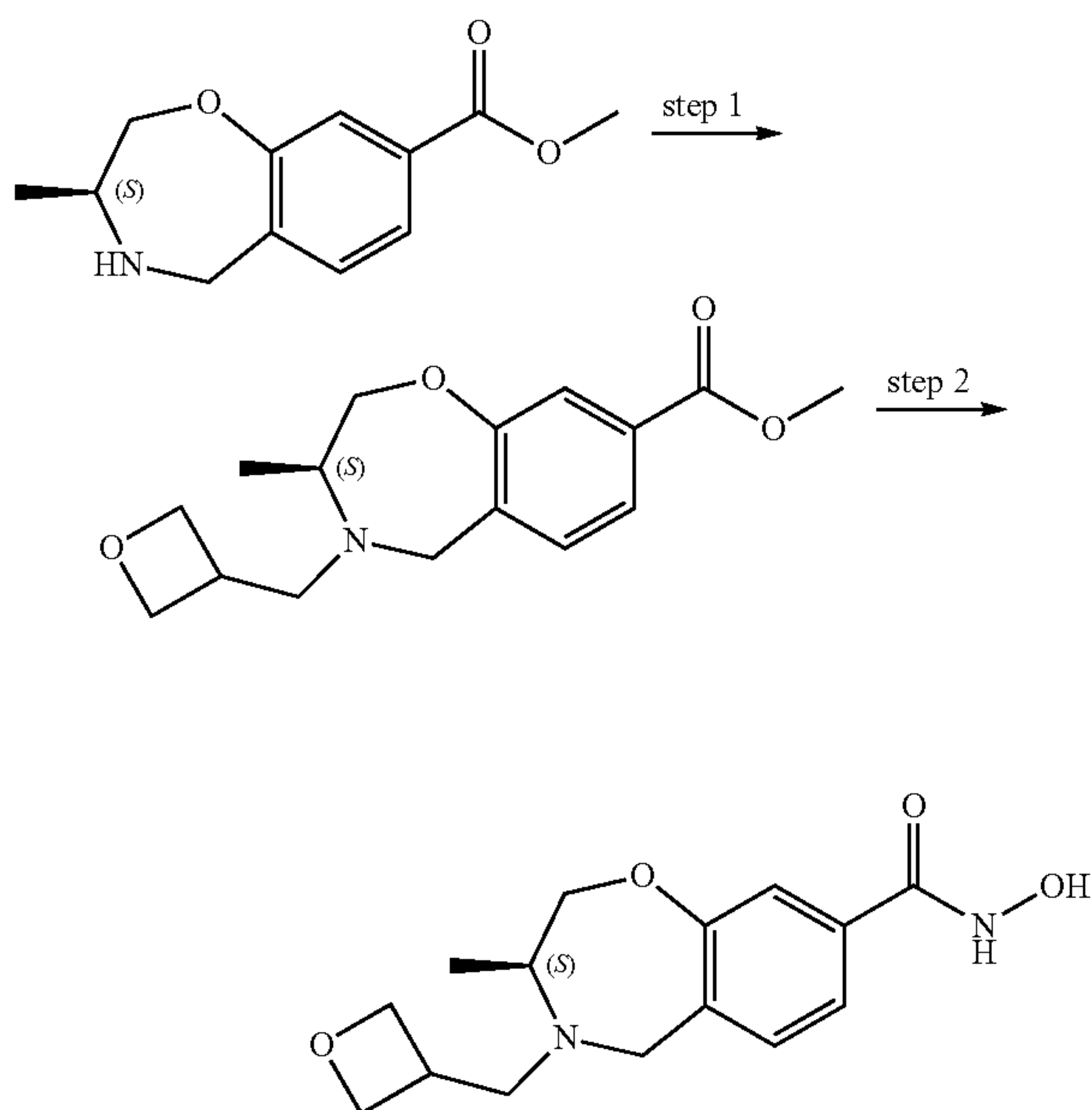


Into a 4-mL vial was added methyl (S)-3-methyl-4-(oxetan-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (29.6 mg, 0.081 mmol, 1 equiv),  $\text{NH}_2\text{OH}$  (50% in water, 107  $\mu\text{L}$ , 1.62 mmol, 20 equiv) and aq. 1N NaOH (324  $\mu\text{L}$ , 0.162 mmol, 4 equiv) in a solution of THF/MeOH (4:1, 1.0 mL). The resulting solution was allowed to stir at room temperature for 16 hours. The reaction was concentrated to dryness and purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5  $\mu\text{m}$ , 19 $\times$ 50 mm; Mobile Phase A: Water/0.1% formic acid; Mobile Phase B: MeCN/0.1% formic acid; Flow rate: 23 mL/min; Gradient: 0% B to 35% B in 8 min; Detector: UV 254, 220 nm) to afford the title compound as a light brown oil (34.4 mg, 53% yield).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.16 (s, 1H), 9.45 (br s, 1H), 9.02 (s, 1H), 8.60 (d,  $J=1.2$  Hz, 1H), 7.28-7.39 (m, 1H), 7.25 (d,  $J=1.8$  Hz, 1H), 7.17 (br d,  $J=7.6$  Hz, 1H), 4.77 (quin,  $J=6.3$  Hz, 1H), 4.32-4.49 (m, 2H), 4.22 (br d,  $J=15.8$  Hz, 1H), 3.76-4.11 (m, 2H), 3.34 (s, 6H), 2.94 (s, 2H), 2.78 (s, 2H), 2.37-2.58 (m, 3H), 1.86-1.96 (m, 2H), 1.12-1.20 (m, 1H), 1.01-1.25 (m, 3H), 1.01-1.07 (m, 1H). MS: (ES,  $m/z$ ): 279  $[\text{M}+\text{H}]^+$ .

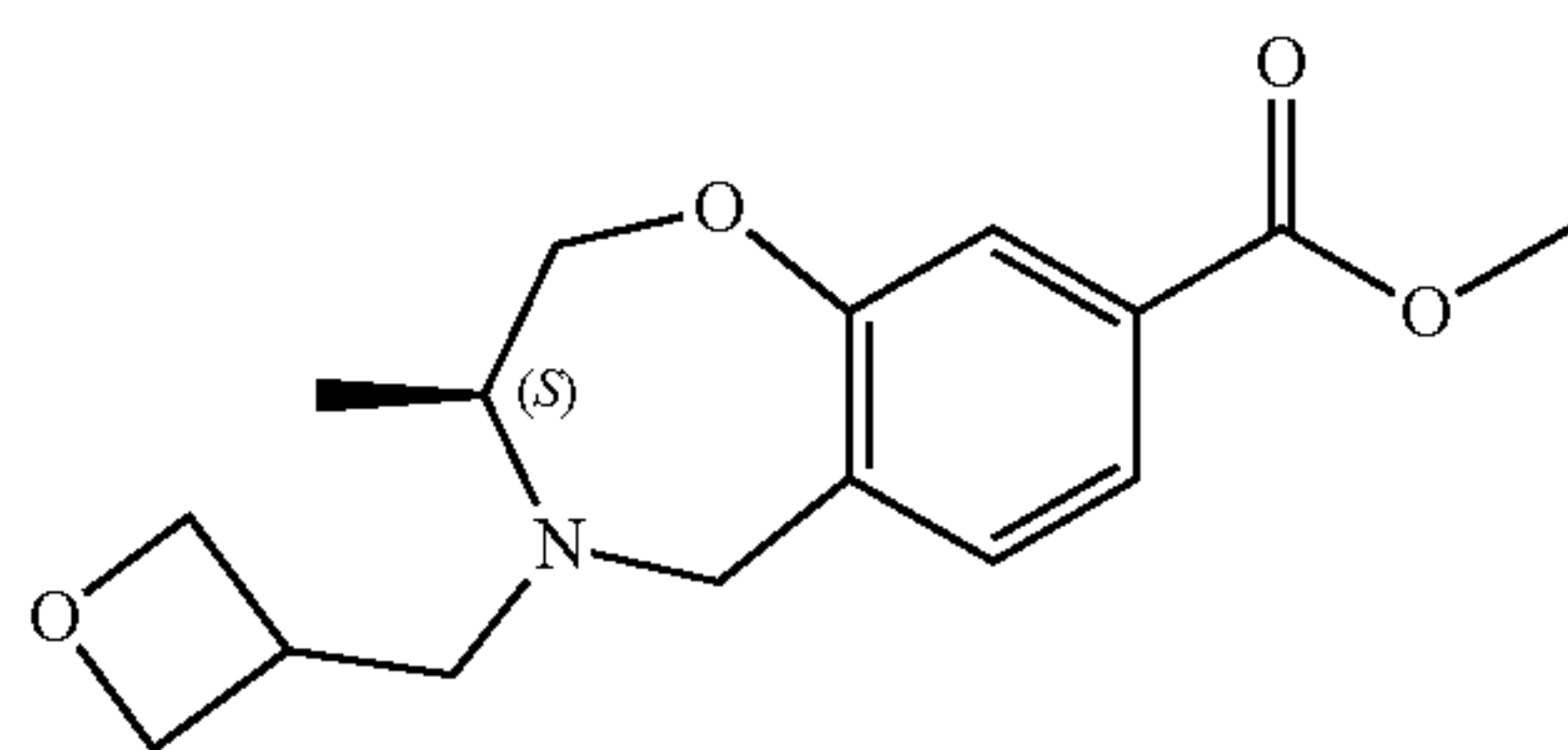
## 137

## Example 46

Preparation of (S)—N-hydroxy-3-methyl-4-(oxetan-3-ylmethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



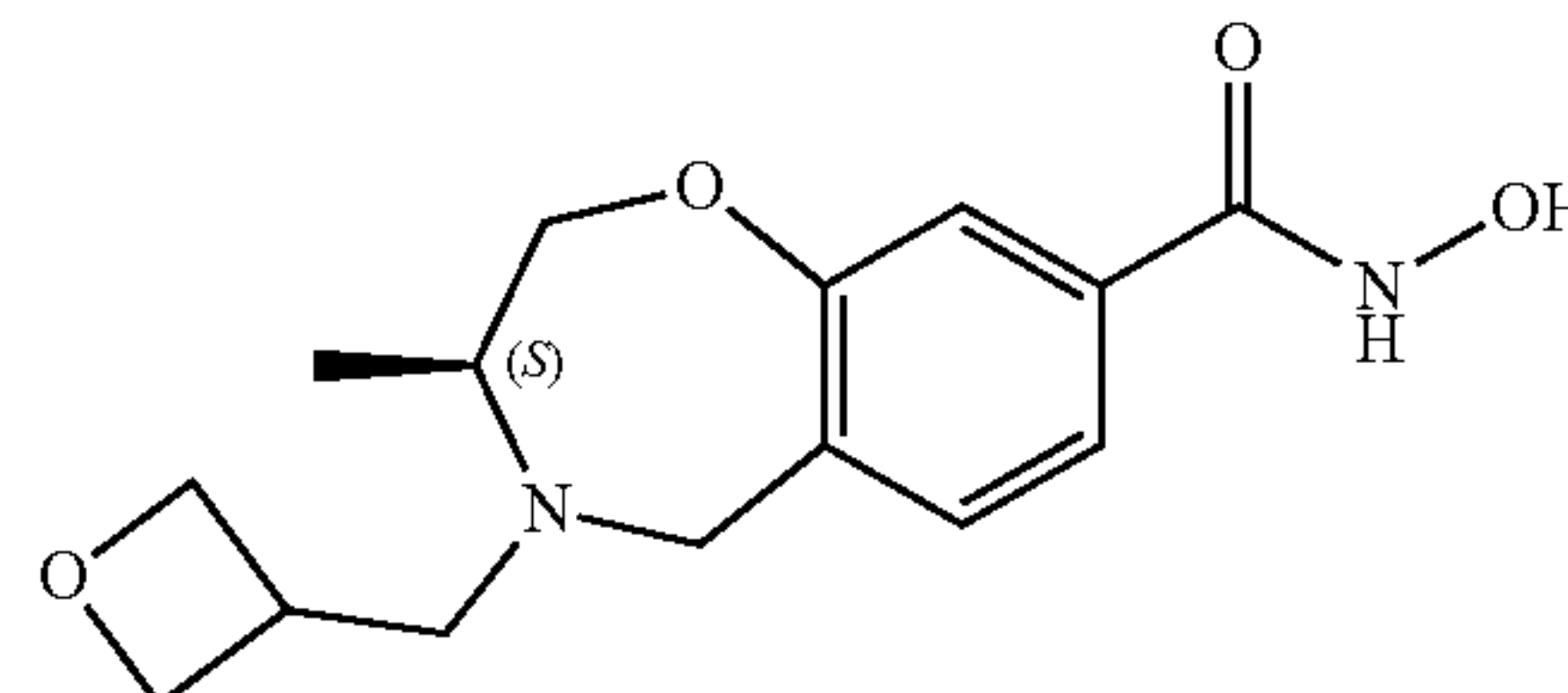
Step-1: Methyl (S)-3-methyl-4-(oxetan-3-ylmethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 100-mL round-bottom flask, were placed methyl (S)-3-methyl-4-(oxetan-3-ylmethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (150 mg, 0.68 mmol, 1 equiv) and acetic acid (5 mL). To this was added oxetane-3-carbaldehyde (117 mg, 1.36 mmol, 2 equiv). The resulting solution was stirred for 1.5 h at room temperature. This was followed by the addition of acetyl ethaneperoxoate sodioboranyl acetate (2.28 g, 10.76 mmol, 10 equiv) in several batches. The resulting solution was stirred for 16 h at room temperature, then concentrated under vacuum. The residue was dissolved in EtOAc (100 mL) and washed with H<sub>2</sub>O (4×30 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:20) to afford the title compound as a yellow solid (48 mg, 24% yield. MS: (ES, m/z): 292 [M+H]<sup>+</sup>.

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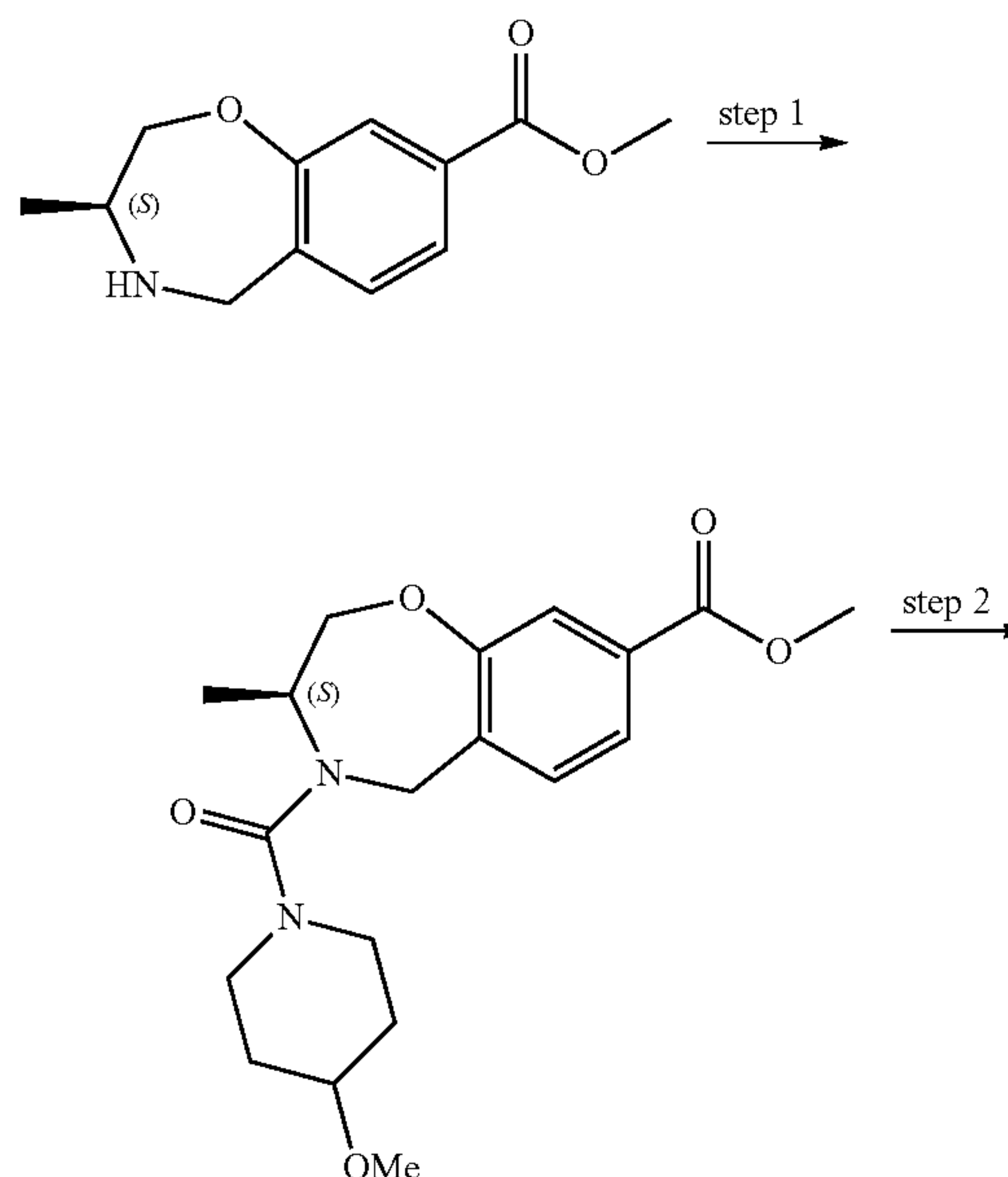
Step-2: (S)—N-Hydroxy-3-methyl-4-(oxetan-3-ylmethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, were placed methyl (S)-3-methyl-4-(oxetan-3-ylmethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (60 mg, 0.21 mmol, 1 equiv) and THF/MeOH (4:1, 1.5 mL). Then a solution of NH<sub>2</sub>OH (50% in water, 0.42 mL, 30 equiv) and a solution of sodium hydroxide (1 mol/L, 0.42 mL, 2 equiv) were added at the same time. The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge RP C18 OBD, 5 μm, 19×100 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 4% B to 58% B in 7 min; Detector: UV 254, 220 nm) to afford the title compound as a yellow solid (9 mg, 11% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.35 (br s, 1H), 10.30-10.01 (br s, 1H), 9.14 (br s, 1H), 7.52-7.24 (m, 3H), 4.65-4.64 (d, J=5.2 Hz, 3H), 4.51-3.76 (m, 8H), 3.57-3.45 (m, 1H), 1.49-1.15 (m, 3H). MS: (ES, m/z): 293 [M+H]<sup>+</sup>.

## Example 47

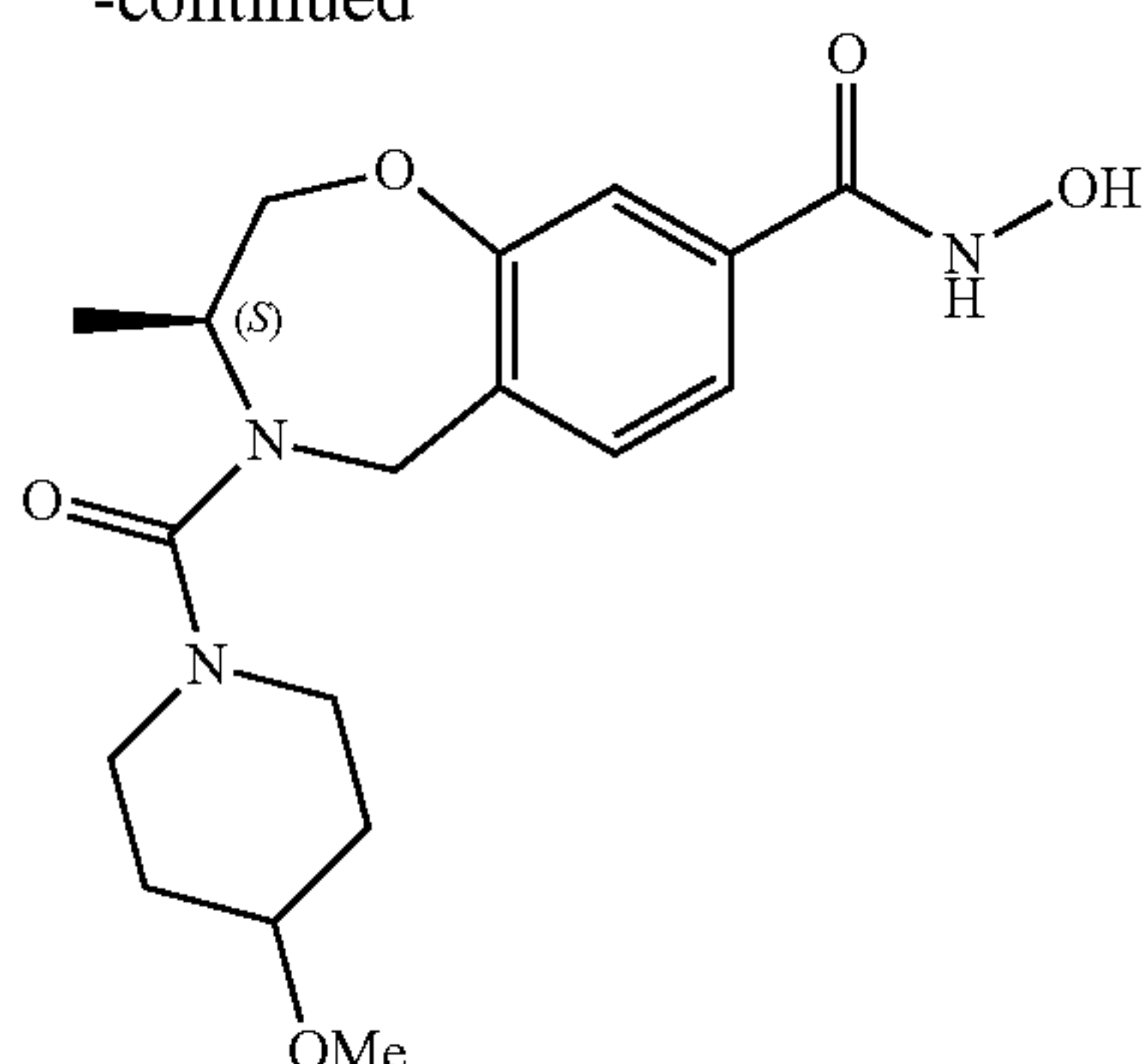
Preparation of (S)—N-hydroxy-4-(4-methoxypiperidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



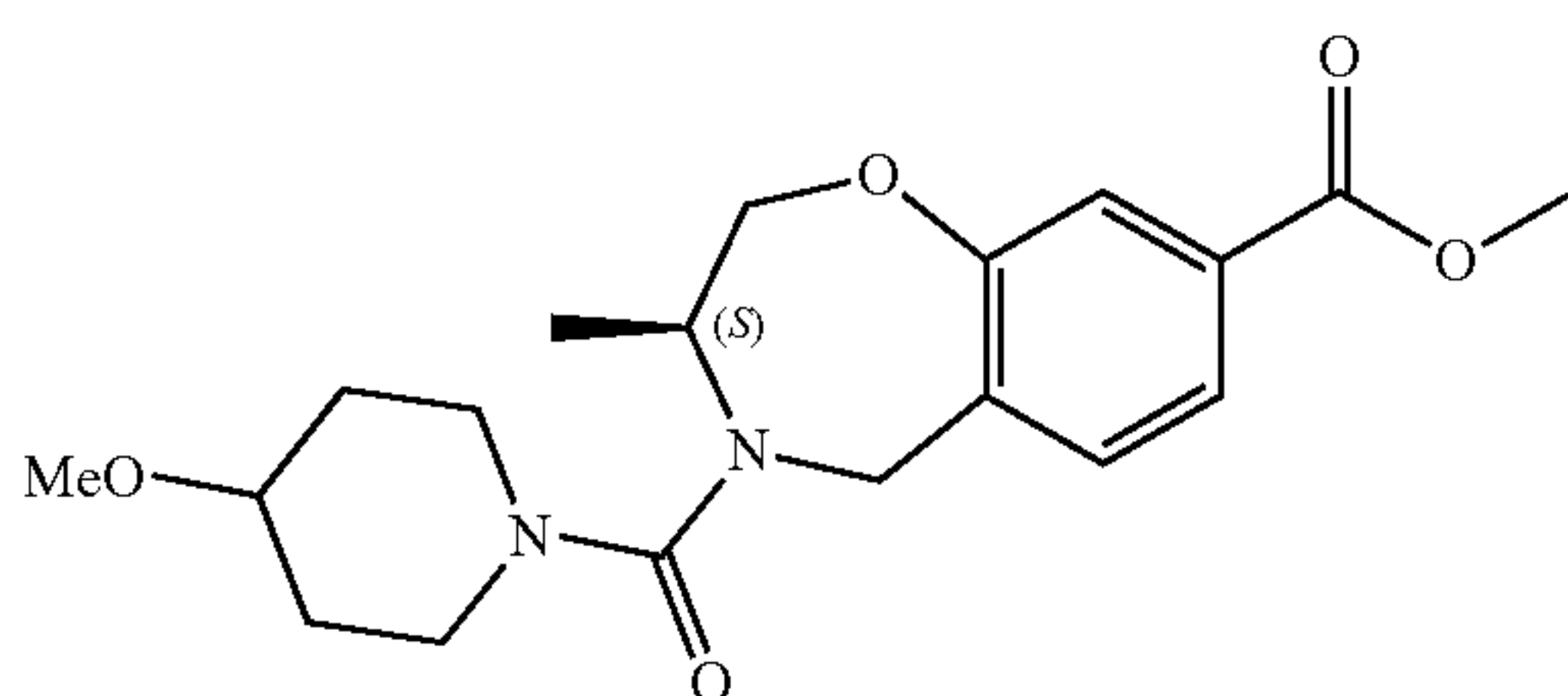


**139**

-continued

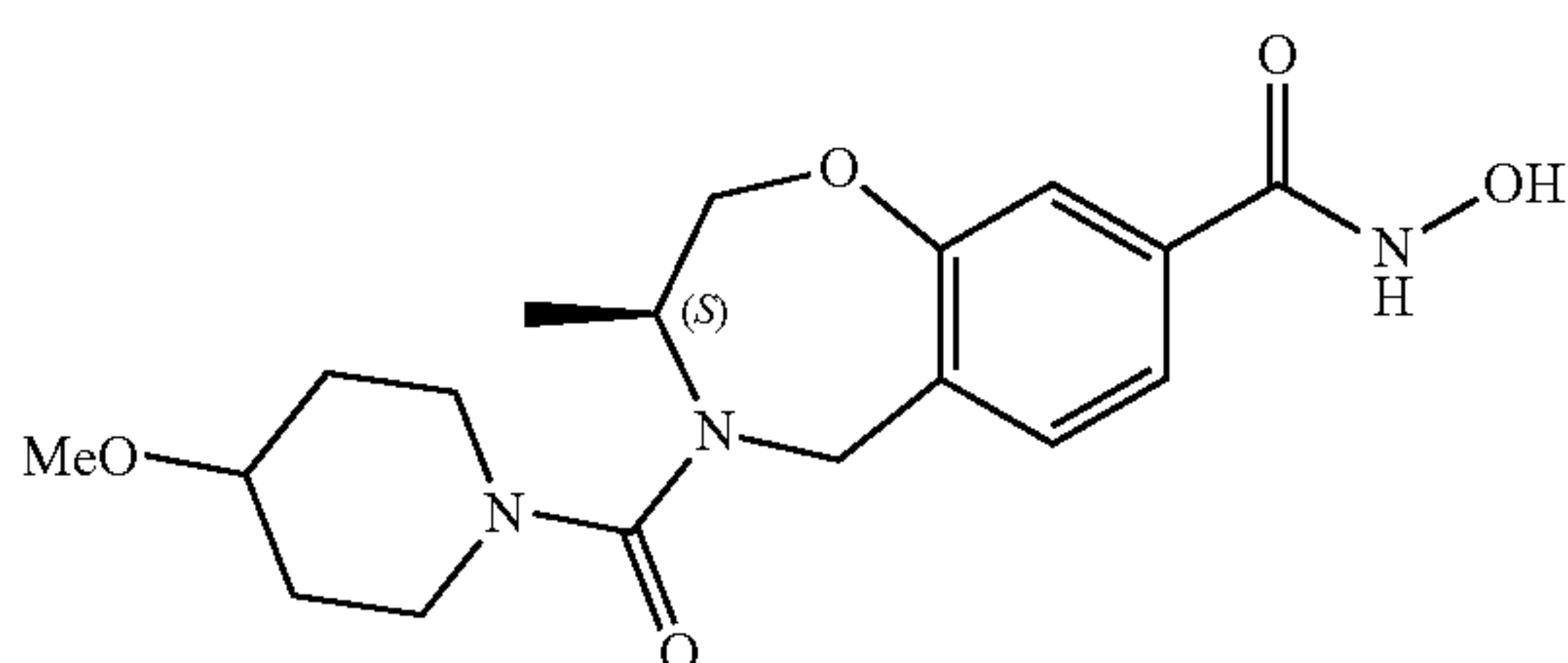


Step-1: Methyl (S)-4-(4-methoxypiperidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 25-mL round-bottom flask, was placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.45 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (10 mL), triphosgene (44 mg, 0.16 mmol, 0.33 equiv), the resulting solution was stirred for 10 min at 25° C. Then  $\text{Et}_3\text{N}$  (91 mg, 0.90 mmol, 2 equiv) was added into the solution at 0° C. and was stirred for 20 min at 25° C. Then a solution of 4-methoxypiperidine (208 mg, 1.81 mmol, 4 equiv) in  $\text{CH}_2\text{Cl}_2$  was added and the reaction was stirred for 30 min at 25° C. The resulting solution was diluted with  $\text{H}_2\text{O}$  (20 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3×15 mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under vacuum to afford the title compound as yellow oil (150 mg) which was used without further purification. MS: (ES, m/z): 363  $[\text{M}+\text{H}]^+$ .

Step-2: (S)-N-Hydroxy-4-(4-methoxypiperidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



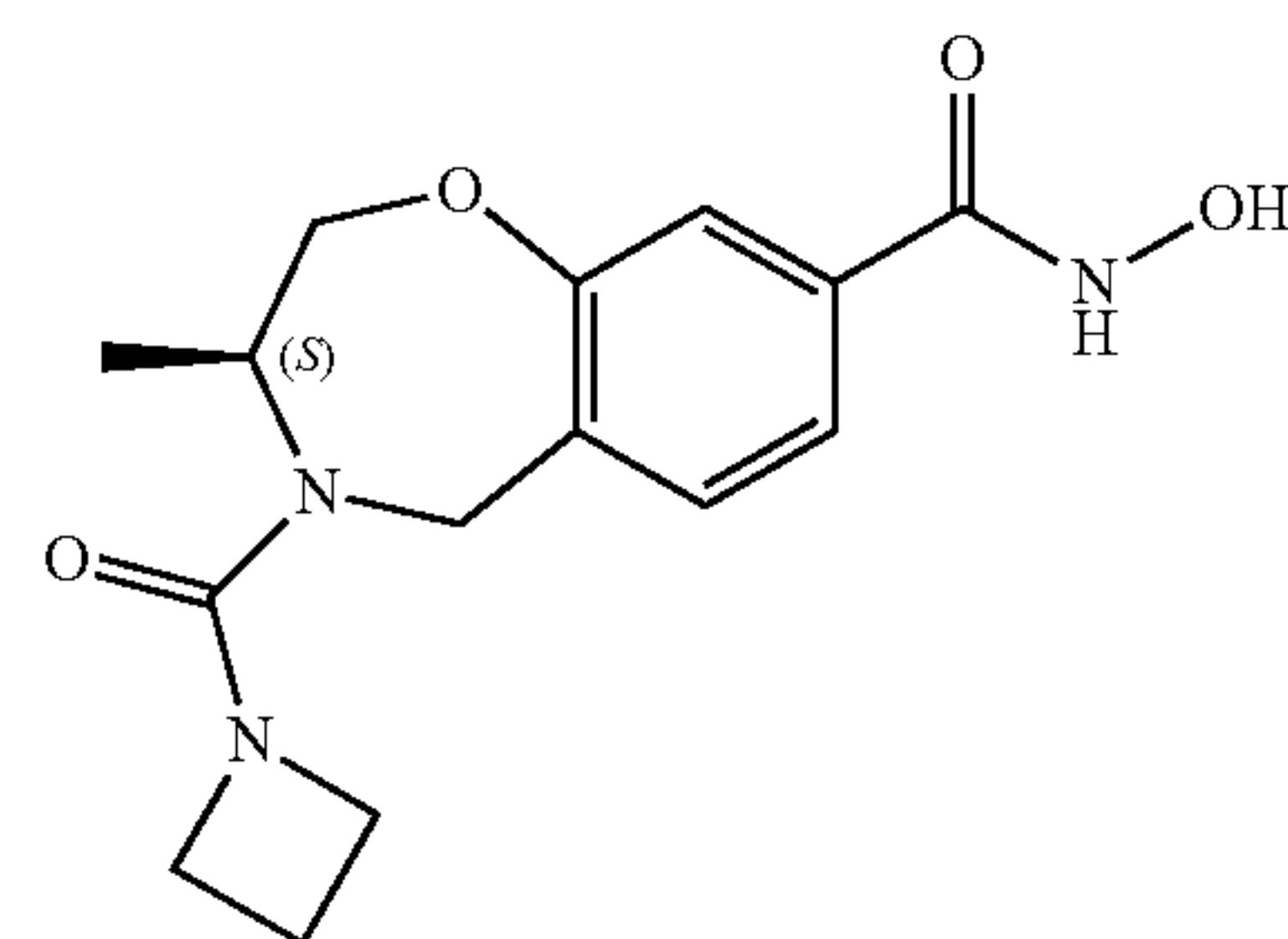
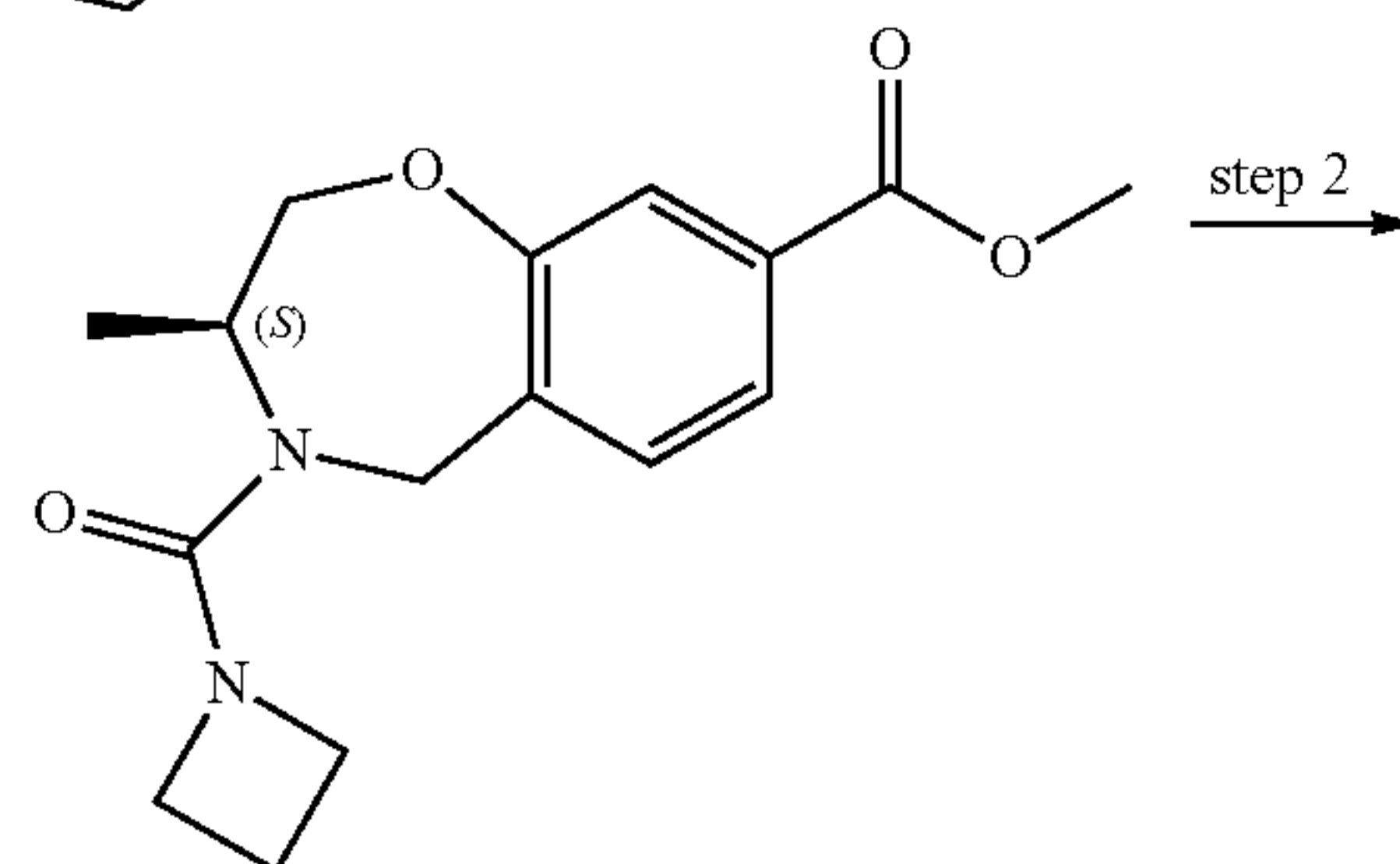
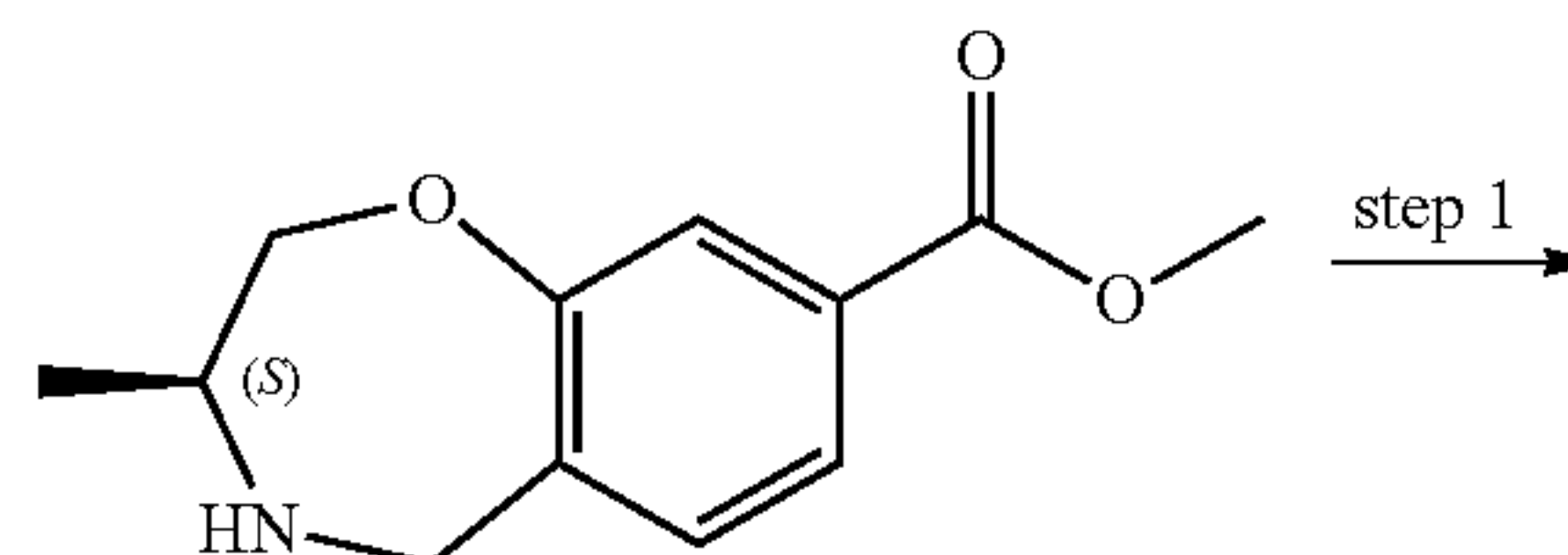
Into a 10-mL round-bottom flask, was placed methyl (S)-4-(4-methoxypiperidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (150 mg,

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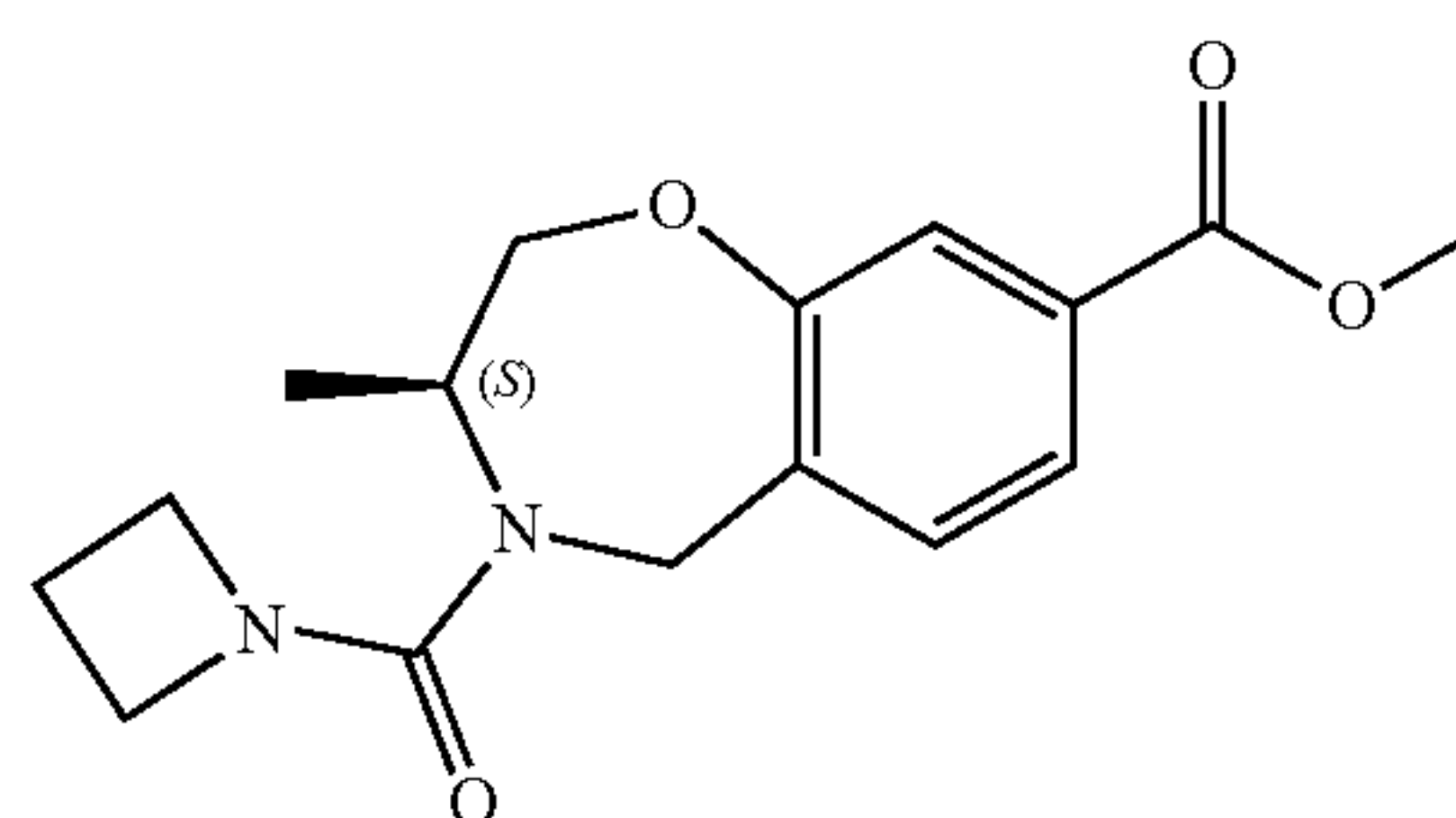
0.41 mmol, 1 equiv),  $\text{NH}_2\text{OH}$  (50% in water, 1.62 g, 49 mmol, 120 equiv), and aq. 1N NaOH (33 mg, 0.83 mmol, 2 equiv). The resulting solution was stirred for 2 h at 25° C. The crude product was purified by Prep-HPLC (Column: Sunfire Prep C18 OBD, 5  $\mu\text{m}$ , 19×150 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 23 mL/min; Gradient: 20% B to 30% B in 8 min; Detector: UV 254, 220 nm) to afford the title compound as a light pink solid (29.5 mg, 20% yield).  $^1\text{H}$ -NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$ (ppm): 11.11 (s, 1H), 9.01 (s, 1H), 7.34-7.21 (m, 3H), 4.60-4.55 (d,  $J=17.1$  Hz, 1H), 4.32-4.26 (d,  $J=16.8$  Hz, 1H), 4.16-4.03 (m, 3H), 3.26-3.21 (m, 6H), 2.81-2.68 (m, 2H), 1.84-1.70 (m, 2H), 1.43-1.29 (m, 2H), 1.19 (s, 3H). MS: (ES, m/z): 364  $[\text{M}+\text{H}]^+$ .

Example 48

Preparation of (S)-4-(azetidine-1-carbonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



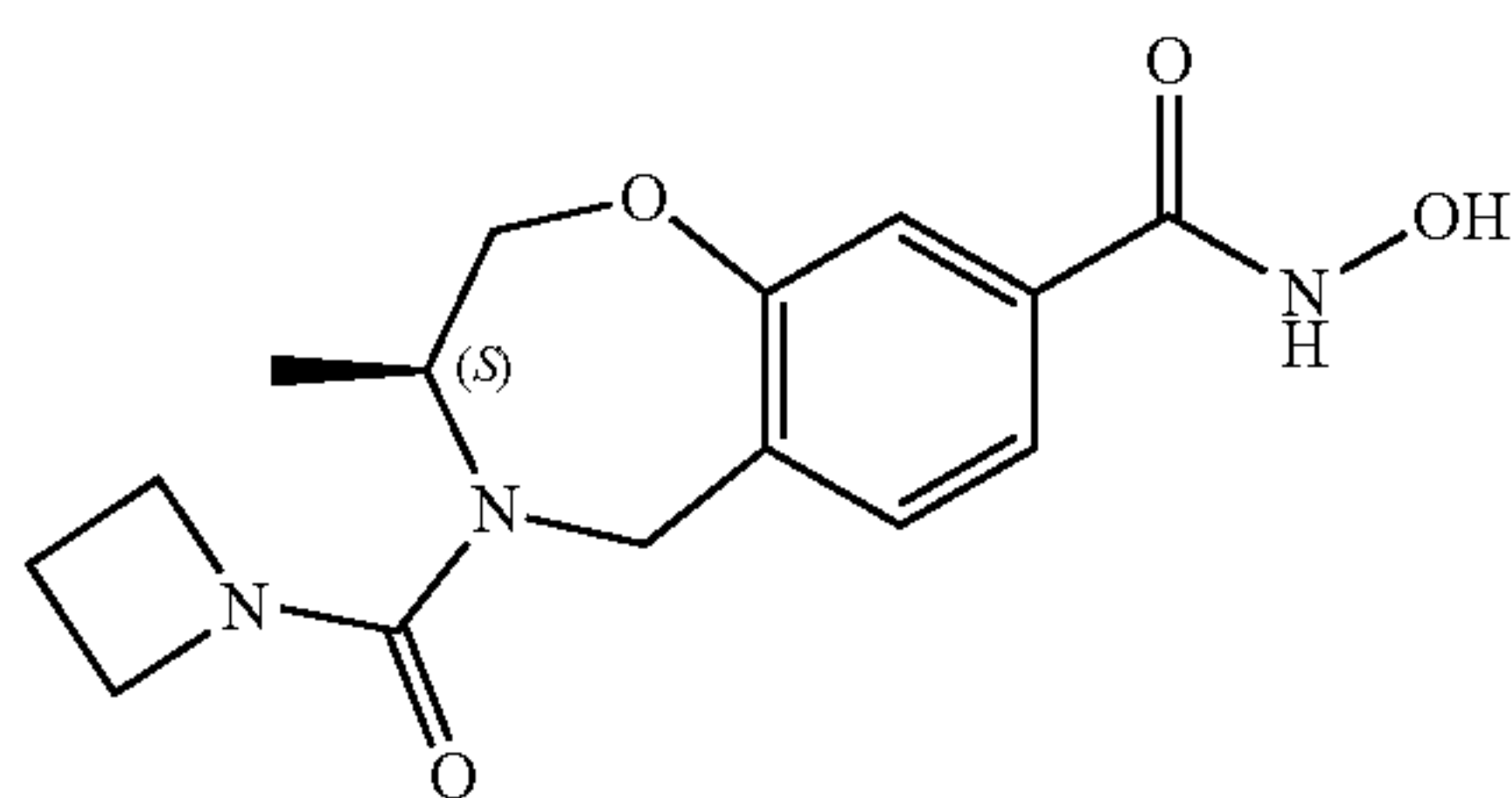
Step-1: Methyl (S)-4-(azetidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



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Into an 8 mL vial were added triphsogene (34.5 mg, 0.116 mmol, 0.4 equiv) in  $\text{CH}_2\text{Cl}_2$  (2 mL). A solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate hydrochloride (75 mg, 0.194 mmol, 1 equiv),  $\text{Et}_3\text{N}$  (0.162 mL, 1.164 mmol, 4 equiv) and azetidine hydrochloride (27.2 mg, 0.291 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added to the stirring solution. This solution was stirred at room temperature for 16 hours. The reaction was quenched with brine (2 mL) and concentrated to dryness. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5  $\mu\text{m}$ , 19 $\times$ 50 mm; Mobile Phase A: Water/0.1% formic acid; Mobile Phase B: MeCN/0.1% formic acid; Flow rate: 23 mL/min; Gradient: 15% B to 65% B in 8 min; Detector: UV 254, 220 nm) to afford the title compound as a white solid (16.3 mg, 18% yield). MS: (ES, m/z): 305  $[\text{M}+\text{H}]^+$ .

Step-2: (S)-4-(Azetidine-1-carbonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 4-mL vial was added methyl (S)-4-(azetidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (16.3 mg, 0.054 mmol, 1 equiv),  $\text{NH}_2\text{OH}$  (50% in water, 53.1  $\mu\text{L}$ , 1.60 mmol, 20 equiv) and aq. 1N NaOH (107  $\mu\text{L}$ , 0.107 mmol, 4 equiv) in a solution of THF/MeOH (4:1, 1.0 mL). The resulting solution was allowed to stir at room temperature for 16 hours. The reaction was concentrated to dryness and was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5  $\mu\text{m}$ , 19 $\times$ 50 mm; Mobile Phase A: Water/0.1% formic acid; Mobile Phase B: MeCN/0.1% formic acid; Flow rate: 23 mL/min; Gradient: 0% B to 35% B in 8 min; Detector: UV 254, 220 nm) to afford the title compound. MS: (ES, m/z): 306  $[\text{M}+\text{H}]^+$ .

TABLE 22

The following compound was prepared according to the method of Example 48.	
Structure	Found M + H
	(ES, m/z): 336 $[\text{M} + \text{H}]^+$

## 142

TABLE 22-continued

The following compound was prepared according to the method of Example 48.	
Structure	Found M + H
	(ES, m/z): 350 $[\text{M} + \text{H}]^+$
	(ES, m/z): 343 $[\text{M} + \text{H}]^+$
	(ES, m/z): 348 $[\text{M} + \text{H}]^+$
	(ES, m/z): 343 $[\text{M} + \text{H}]^+$
	(ES, m/z): 350 $[\text{M} + \text{H}]^+$



143

TABLE 22-continued

The following compound was prepared according to the method of Example 48.	
Structure	Found M + H
	(ES, m/z): 364 [M + H] <sup>+</sup>
	(ES, m/z): 343 [M + H] <sup>+</sup>
	(ES, m/z): 362 [M + H] <sup>+</sup>
	(ES, m/z): 362 [M + H] <sup>+</sup>
	(ES, m/z): 384 [M + H] <sup>+</sup>

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Example 49

Preparation of cyclopentyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate

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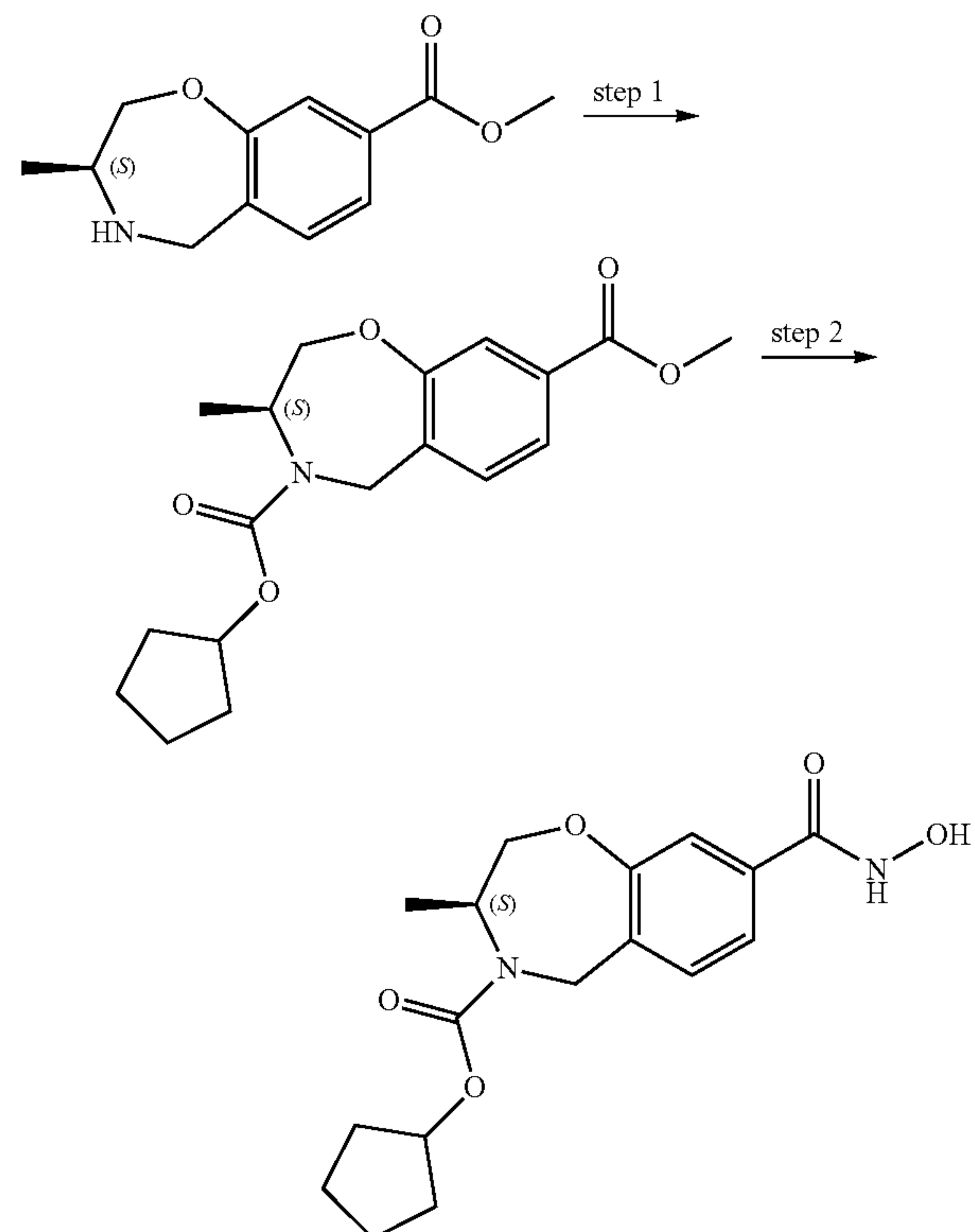
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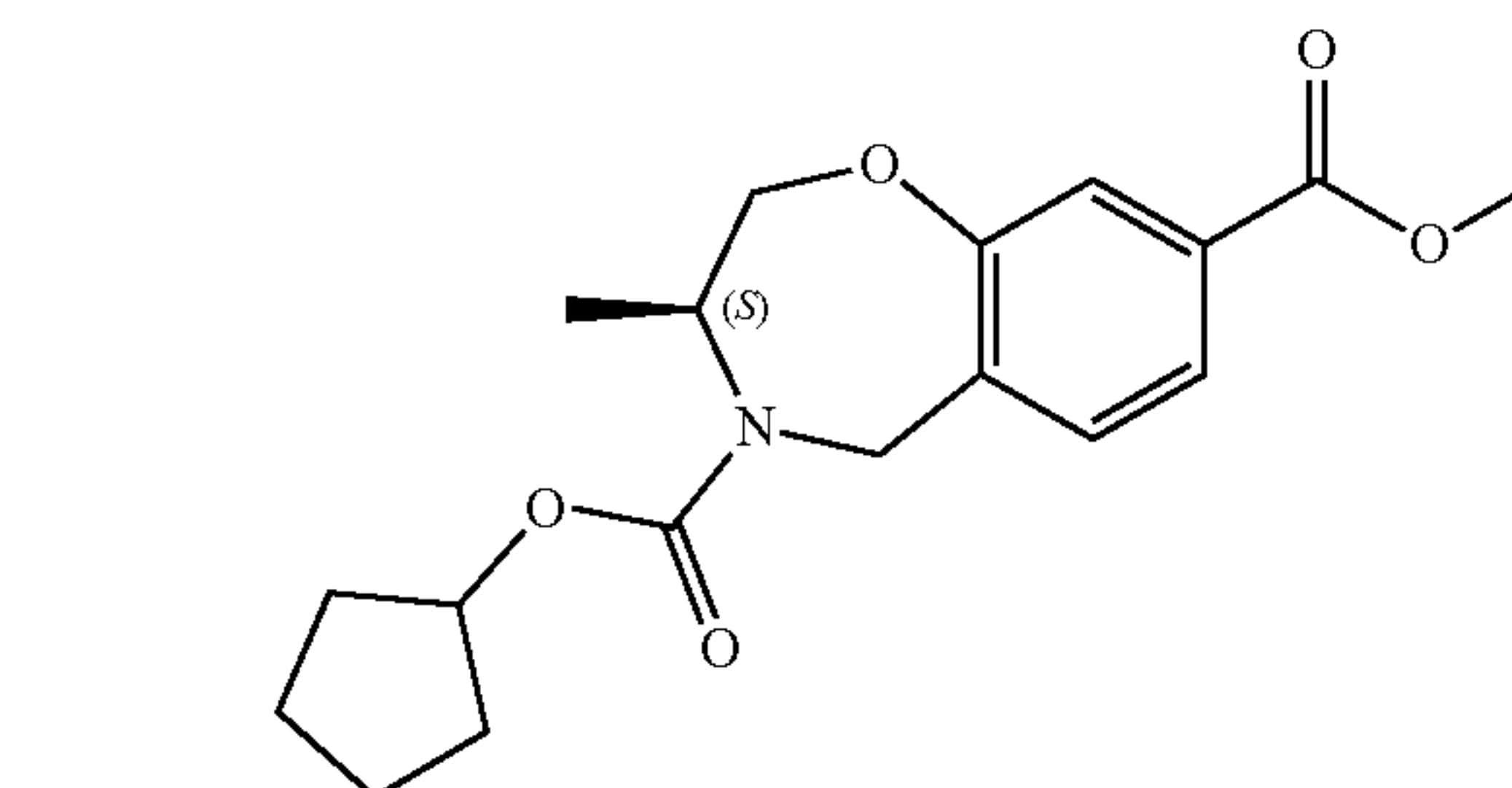
55

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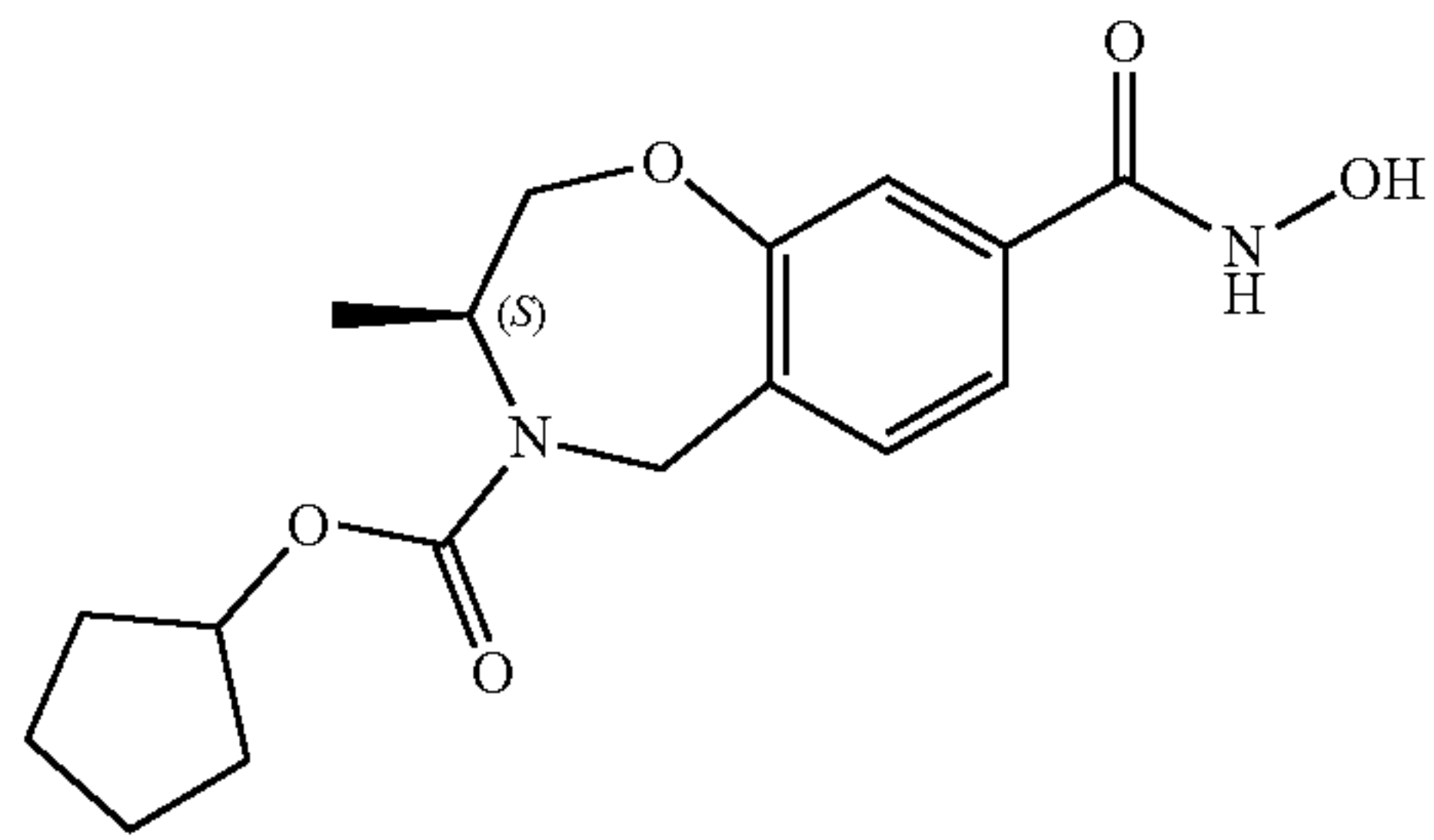
Step-1: 4-Cyclopentyl 8-methyl (S)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxylate



Into a 8-mL vial, was placed a solution of methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate 2,2,2-trifluoroacetate (80 mg, 0.24 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL), Et<sub>3</sub>N (96.9 mg, 0.96 mmol, 4 equiv), cyclopentyl chloroformate (53 mg, 0.36 mmol, 1.5 equiv). The resulting solution was stirred for 5 h at room temperature. The residue was concentrated under vacuum and purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a white solid (40 mg, 50% yield). MS: (ES, m/z): 334 [M+H]<sup>+</sup>.

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Step-2: Cyclopentyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate



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Into a 8-mL vial, was placed a solution of 4-cyclopentyl 8-methyl (S)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxylate (40 mg, 0.12 mmol, 1 equiv) THF/MeOH (4:1, 2.5 mL). Then aq. 1N NaOH (0.30 mL, 2 equiv) and NH<sub>2</sub>OH (50% in water, 0.30 mL, 30 equiv) were added simultaneously. The resulting solution was stirred for 1 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.1% formic acid; Mobile Phase B: MeCN; Flow rate: 20 mL/min; Gradient: 5% B to 65% B in 8 min; Detector: UV 254, 220 nm) to afford the title compound as a white solid (11.7 mg, 29% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.13 (s, 1H), 9.02 (s, 1H), 7.31-7.30 (m, 1H), 7.22-7.18 (m, 2H), 4.96-4.90 (m, 1H), 4.64-4.60 (m, 1H), 4.50-4.39 (m, 2H), 4.24-4.11 (m, 2H), 1.82-1.70 (m, 1H), 1.68-1.55 (m, 5H), 1.32-1.21 (m, 2H), 1.20-1.09 (m, 3H). MS: (ES, m/z): 335 [M+H]<sup>+</sup>.

TABLE 23

The following compound was prepared according to the method of Example 49.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 349 [M + H] <sup>+</sup>	11.13 (br s, 1H), 9.01 (br s, 1H), 7.30 (m, 1H), 7.24-7.19 (m, 2H), 4.65 (m, 1H), 4.50-4.54 (m, 3H), 4.26-4.12 (m, 2H), 1.69-1.60 (m, 3H), 1.42-1.24 (m, 6H), 1.12-1.10 (m, 4H)
	(ES, m/z): 295 [M + H] <sup>+</sup>	11.12 (s, 1H), 9.08-9.02 (s, 1H), 7.32-7.18 (m, 3H), 4.64-4.48 (m, 3H), 4.26-4.11 (m, 2H), 4.04-3.94 (m, 2H), 1.16-0.99 (m, 6H)
	(ES, m/z): 361 [M + H] <sup>+</sup>	11.14 (br s, 1H), 9.08-9.02 (br s, 1H), 7.34-7.13 (m, 6H), 6.99-6.95 (m 1H), 4.89-4.65 (m, 3H), 4.36-4.20 (m, 2H), 1.27-1.18 (m, 3H)

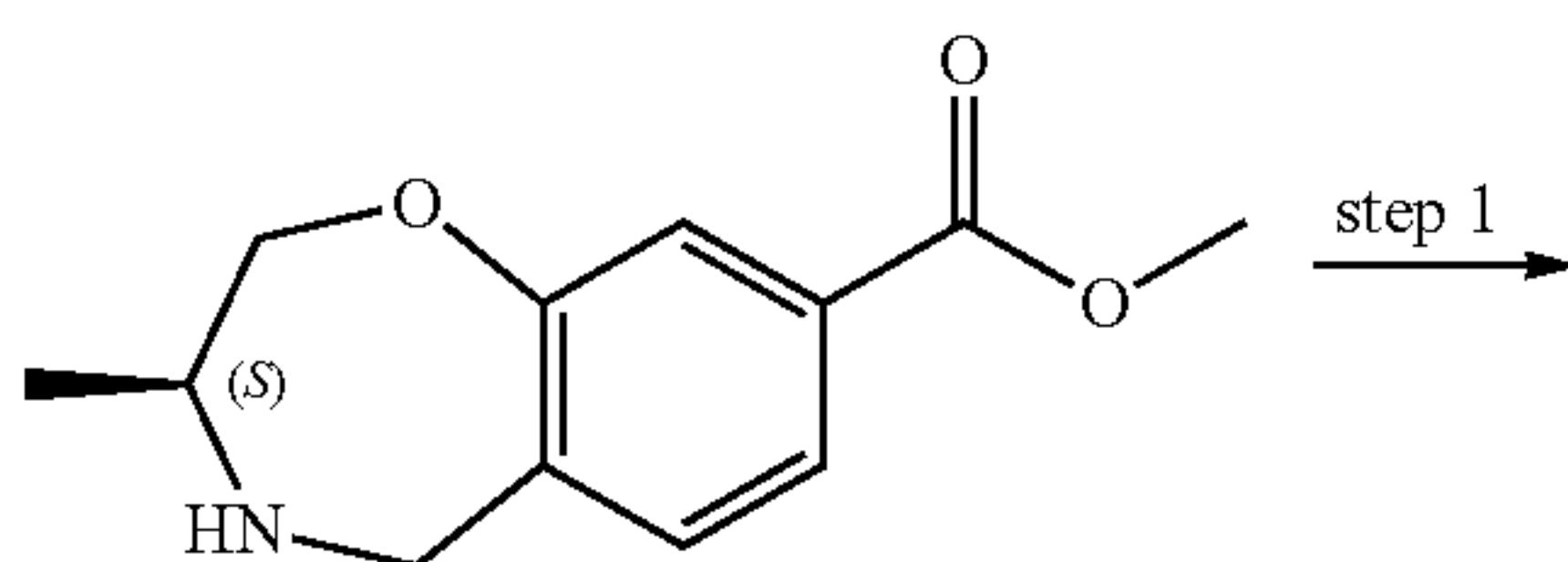


TABLE 23-continued

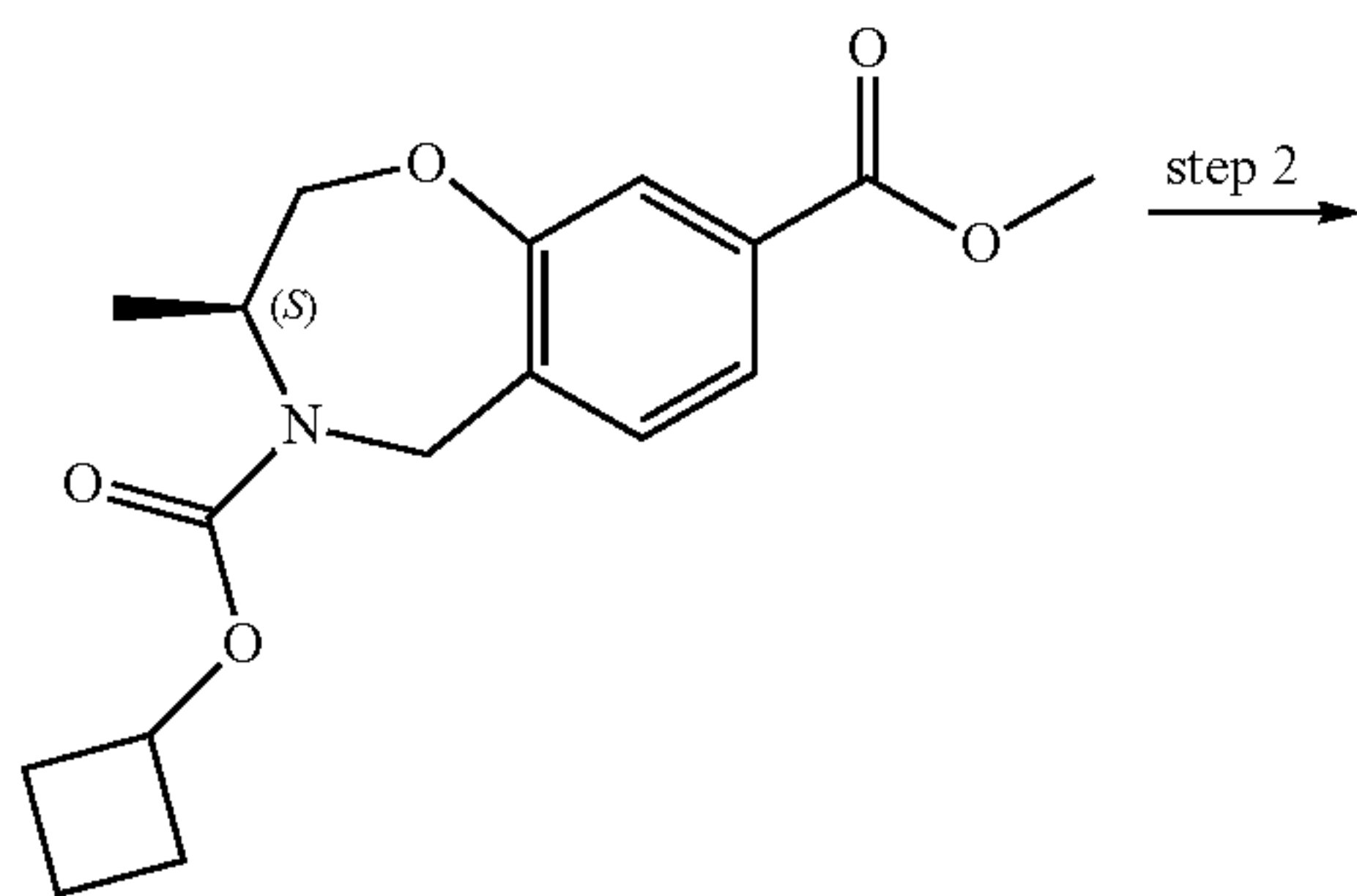
The following compound was prepared according to the method of Example 49.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 11.13 (s, 1H), 8.99 (s, 1H), 7.31-7.18 (m, 3H), 4.70-4.47 (m, 4H), 4.25-4.15 (m, 2H), 1.16-0.92 (m, 9H) 309 [M + H] <sup>+</sup>	

## Example 50

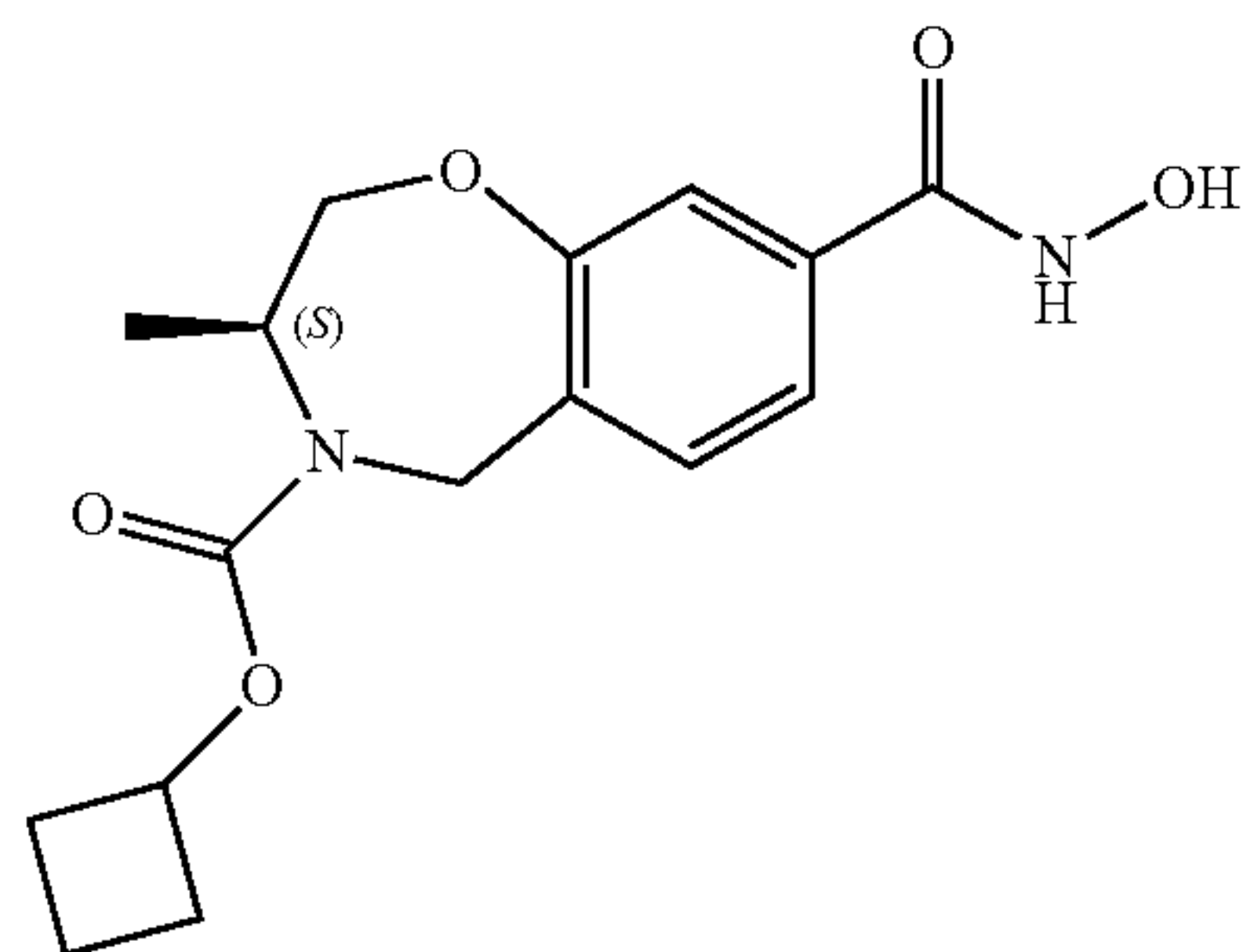
Preparation of cyclobutyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate



step 1



step 2



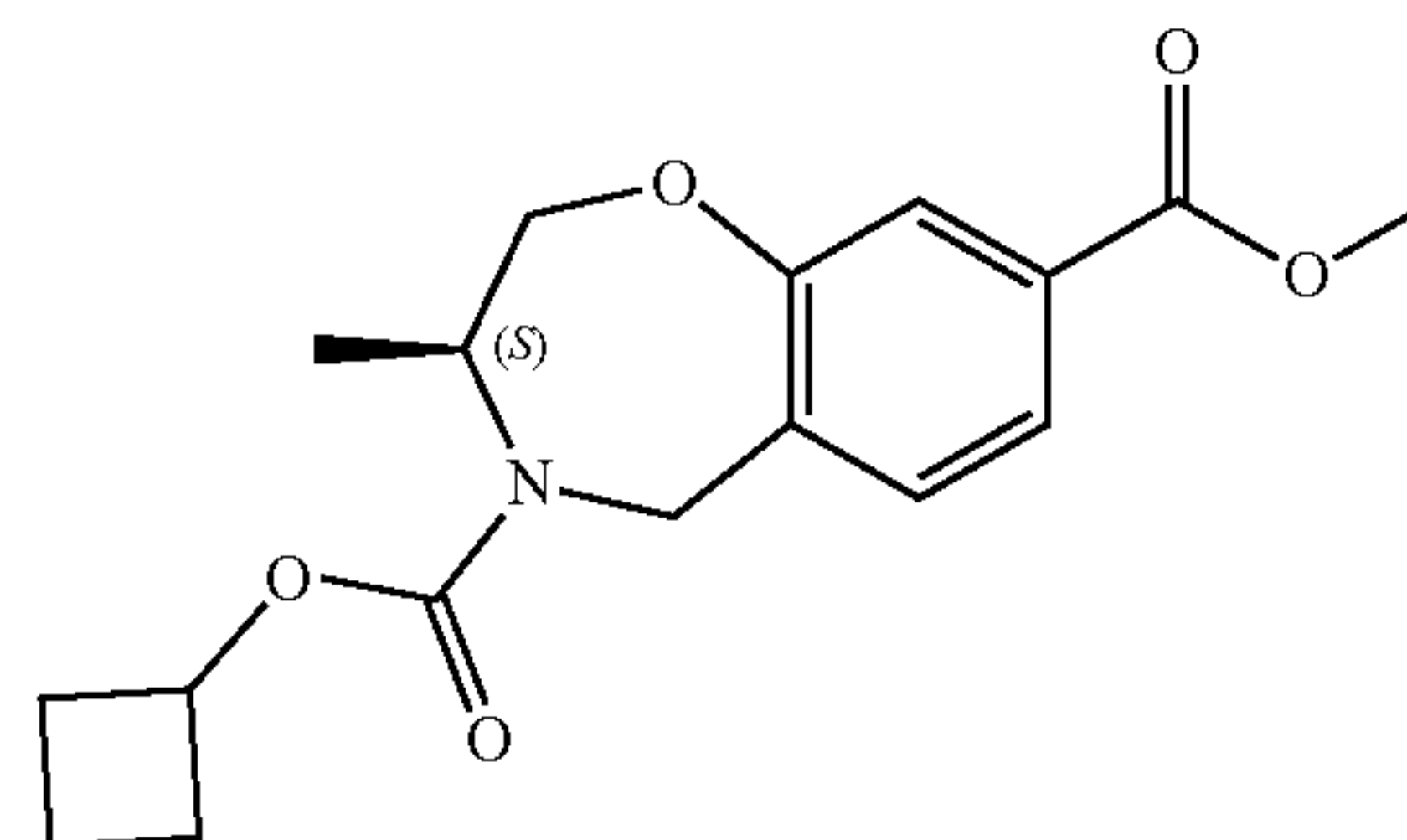
20

Step-1: 4-Cyclobutyl 8-methyl (S)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxylate

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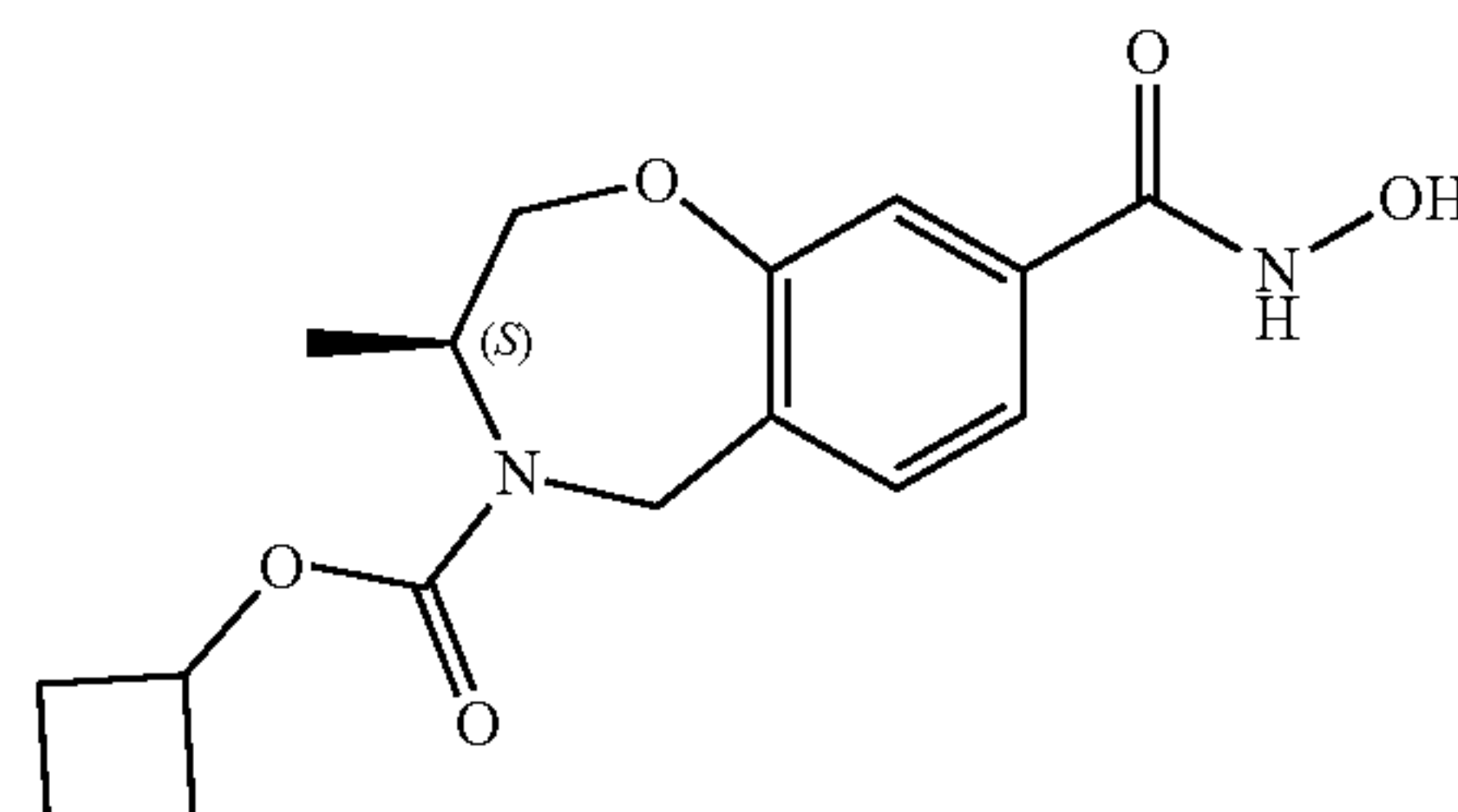
Into a 25-mL round-bottom flask, was placed cyclobutanol (65 mg, 0.90 mmol, 1 equiv), THF (8 mL), triphosgene (90 mg, 0.33 equiv), and Et<sub>3</sub>N (48 mg, 0.47 mmol, 2 equiv). The resulting solution was stirred for 30 min at room temperature. Then, methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (48 mg, 0.22 mmol, 0.24 equiv) was added and the reaction was stirred for 30 min at room temperature. The reaction was then quenched by the addition of water (10 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum to afford the title compound as brown oil (130 mg, 45% yield). MS: (ES, m/z): 320 [M+H]<sup>+</sup>.

Step-2: Cyclobutyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate

55

60

65



## 149

Into a 25-mL round-bottom flask, was placed 4-cyclobutyl 8-methyl (S)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxylate (130 mg, 0.41 mmol, 1 equiv), THF/MeOH (4:1, 3 mL), NH<sub>2</sub>OH (50% in water, 3228 mg, 120 equiv), aq. 1N NaOH (0.82 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The solids were filtered out. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/10 mmol NH<sub>4</sub>HCO<sub>3</sub>; Mobile Phase B: MeCN; Flow rate: 23 mL/min; Gradient: 25% B to 50% B in 7 min; Detector: UV 254, 220 nm) to afford the title compound as a white solid (37.1 mg, 28% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 7.30-7.18 (m, 3H), 4.80-4.57 (m, 3H), 4.44 (s, 1H), 4.25-4.15 (m, 2H), 2.20-2.01 (m, 2H), 1.98-1.92 (m, 1H), 1.67-1.57 (m, 3H), 1.12-1.10 (d, J=6.0 Hz, 3H). MS: (ES, m/z): 321 [M+H]<sup>+</sup>.

## 150

-continued

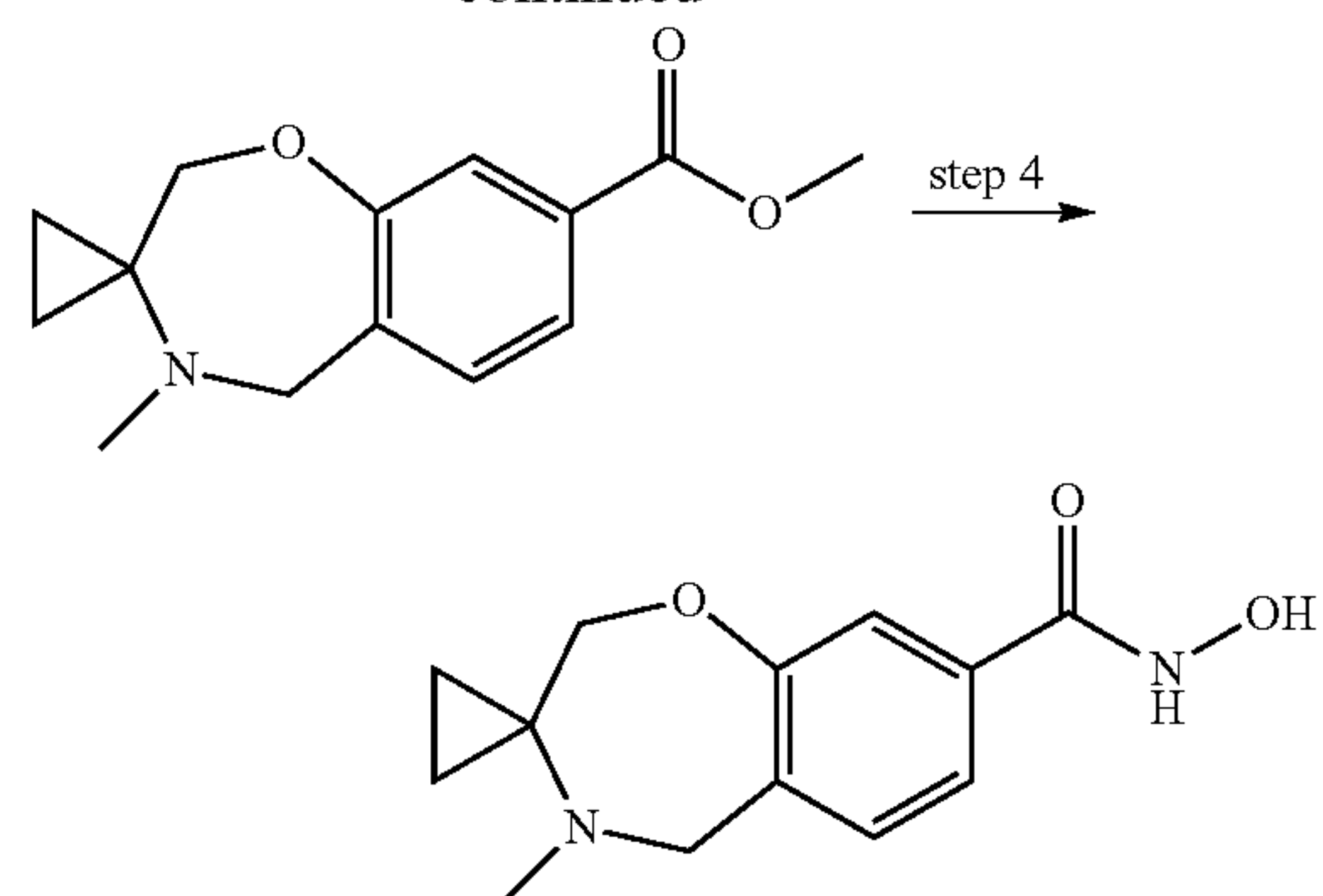
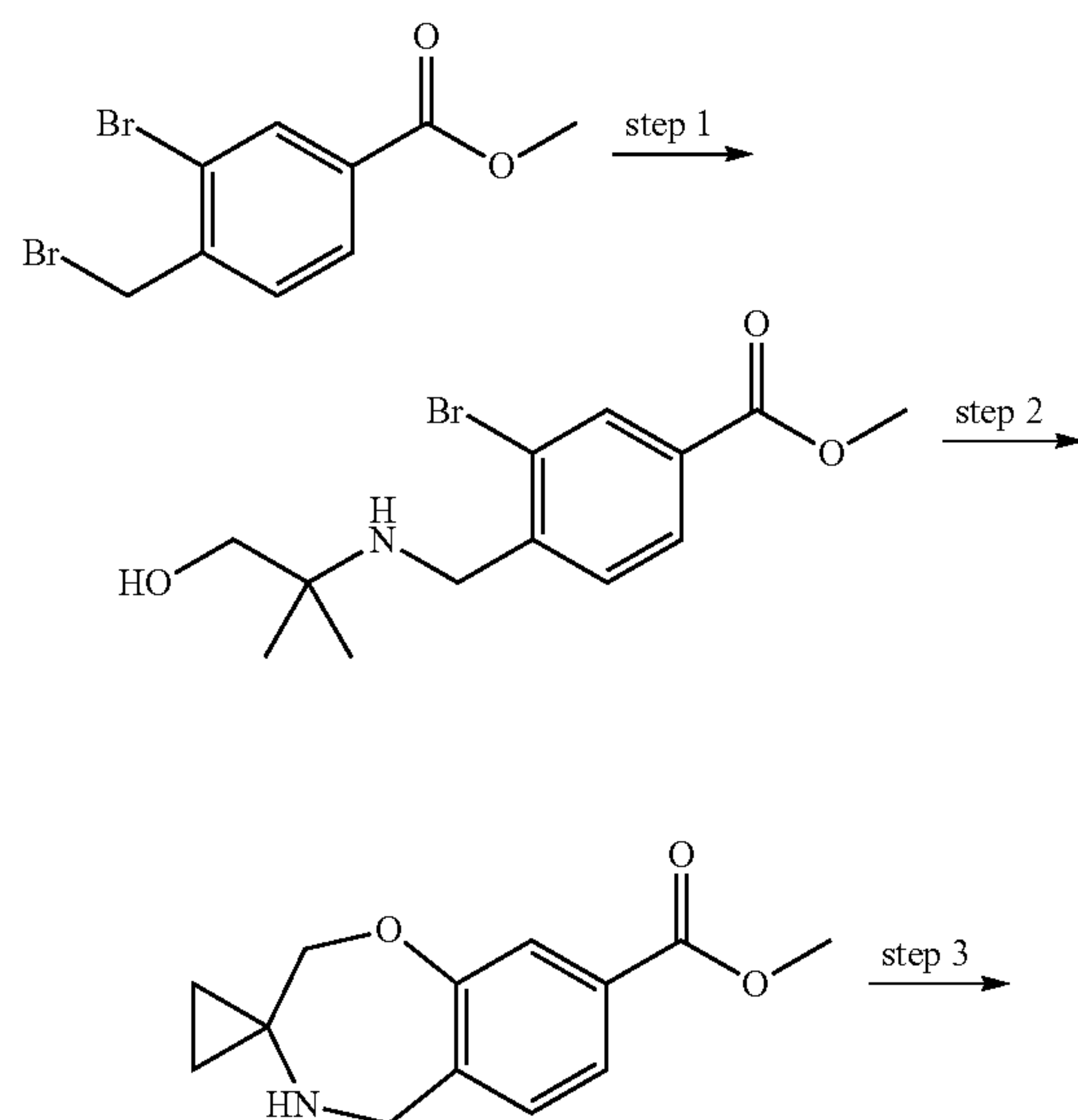


TABLE 24

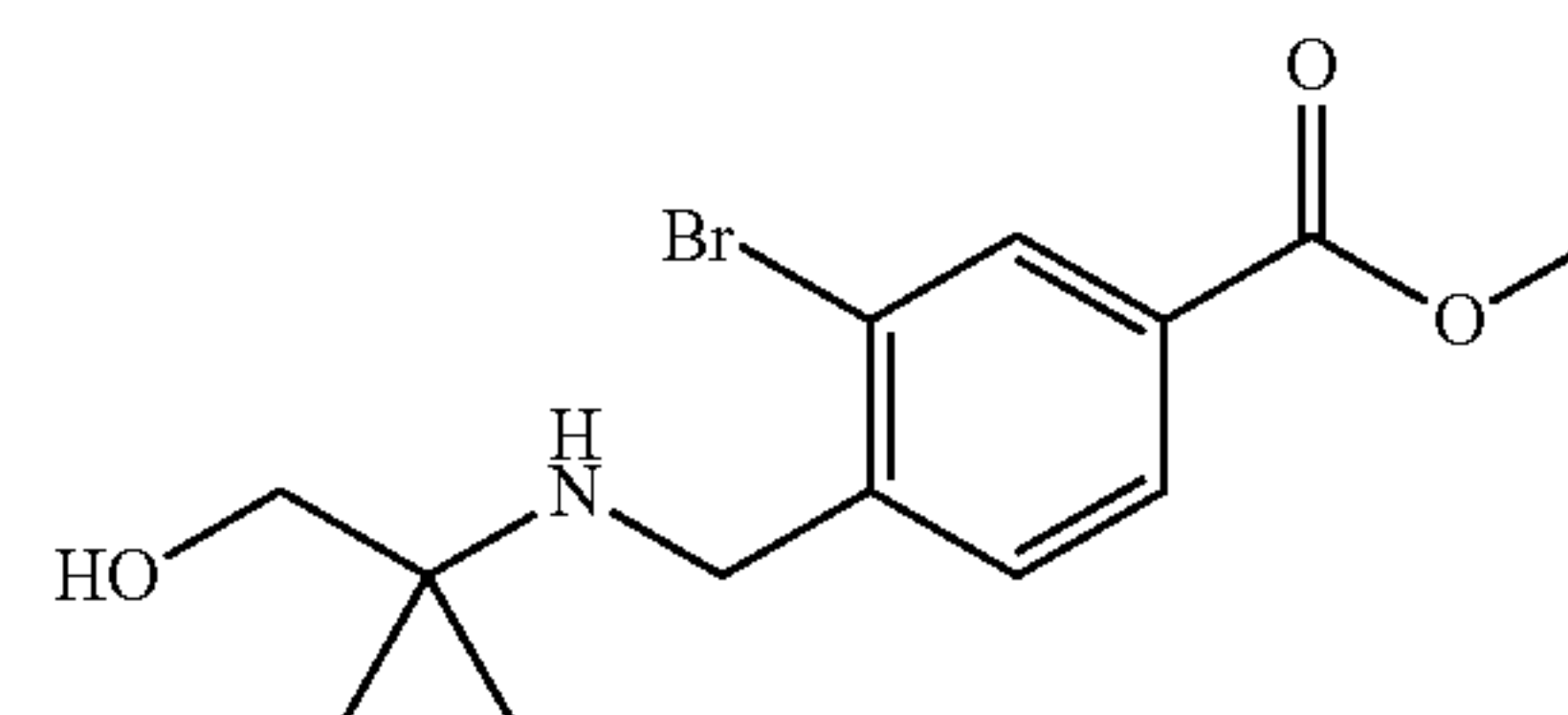
The following compound was prepared according to the method of Example 50.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 11.07 (br s, 1H), 9.07 (br s, 1H), 7.31-7.19 (m, 3H), 4.70-351 4.53 (m, 4H), 4.28-4.17 (m, 2H), 3.74-3.32 (m, 4H), 1.82 (s, [M + H] <sup>+</sup> 2H), 1.53 (s, 2H), 1.21-1.11 (m, 3H)	

## Example 51

Preparation of N-hydroxy-4-methyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxamide



## Step-1: Methyl 3-bromo-4-(((1-(hydroxymethyl)cyclopropyl)amino)methyl)benzoate

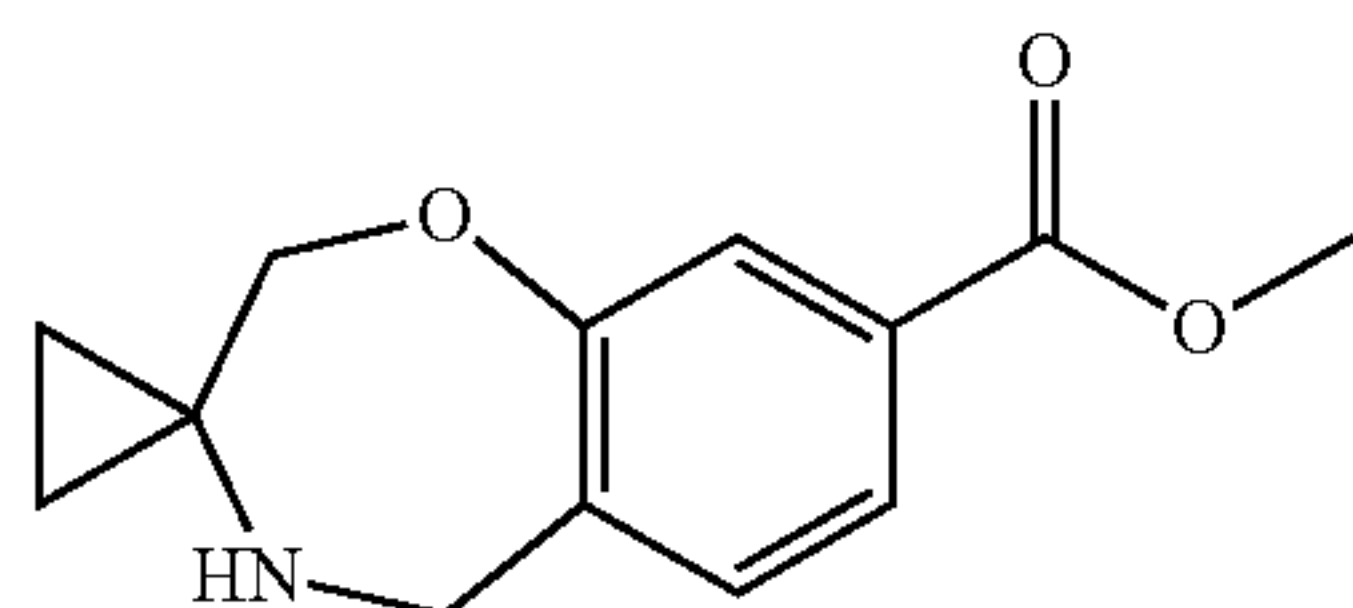


Into a 500-mL round-bottom flask, was placed (1-aminocyclopropyl)methanol hydrochloride (6 g, 48.55 mmol, 2 equiv), K<sub>2</sub>CO<sub>3</sub> (11 g, 79.59 mmol, 3.5 equiv) in MeCN (120 mL). The mixture was stirred at room temperature for 10 min. This was followed by the addition of a solution of methyl 3-bromo-4-(bromomethyl)benzoate (15 g, 48.71 mmol, 1 equiv) in MeCN (150 mL) dropwise with stirring at 0° C. over 2 h. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a yellow oil (7 g, 46% yield). MS: (ES, m/z): 314,316 [M+H]<sup>+</sup>.



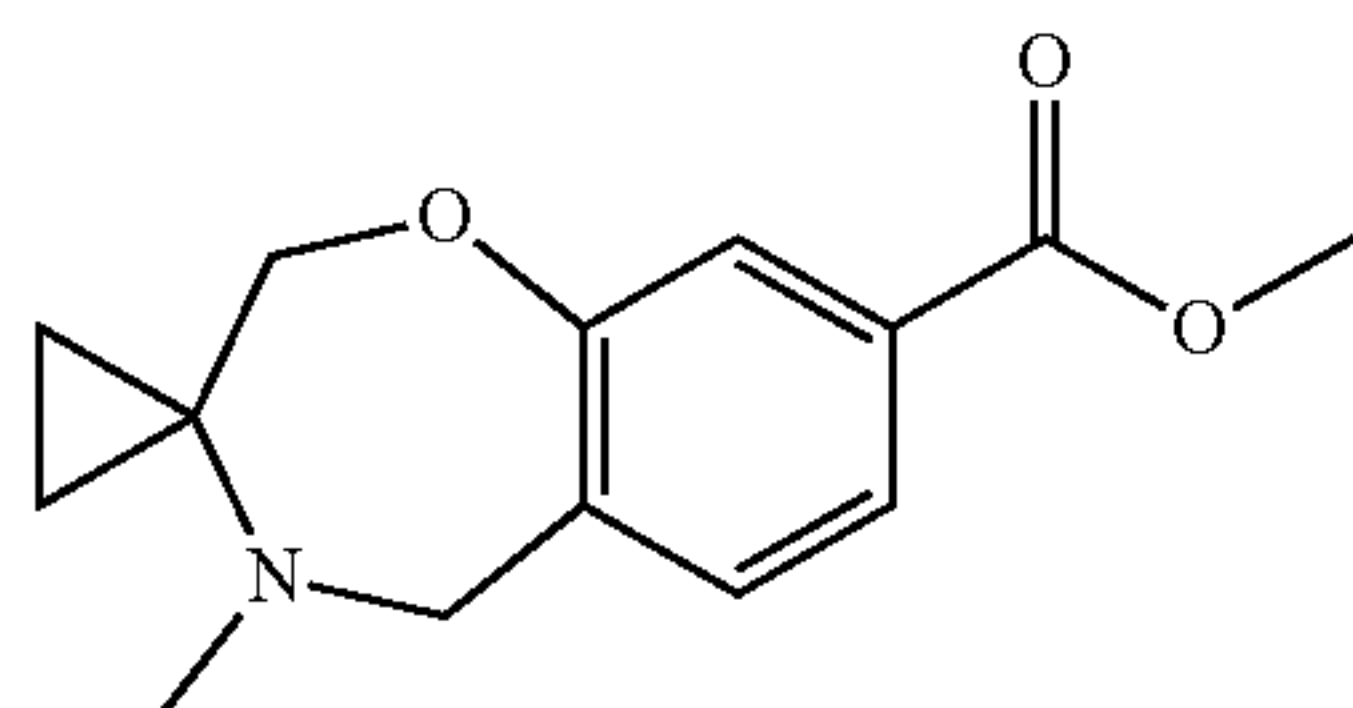
## 151

Step-2: Methyl 4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxylate



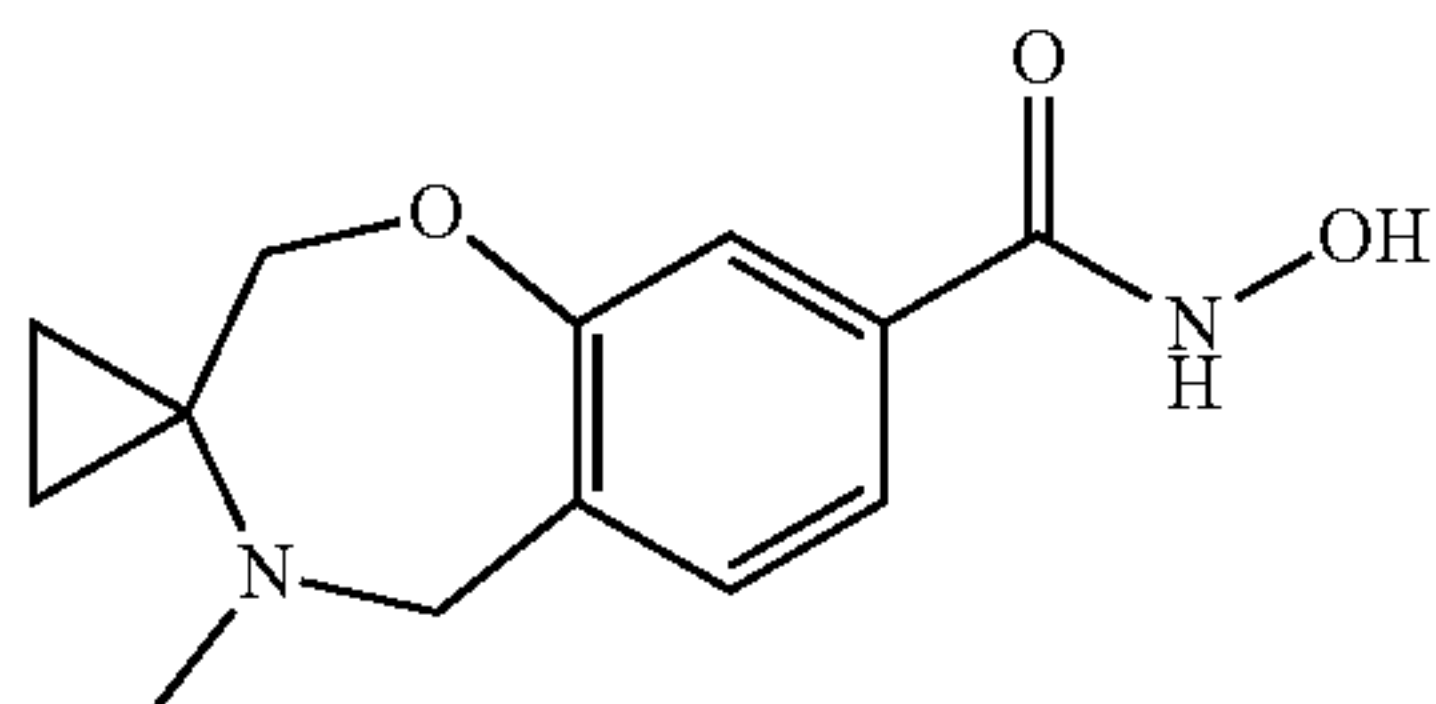
Into a 40-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl 3-bromo-4-(((1-(hydroxymethyl)cyclopropyl)amino)methyl)benzoate (1.5 g, 4.77 mmol, 1 equiv), CuI (273 mg, 1.43 mmol, 0.3 equiv), K<sub>2</sub>CO<sub>3</sub> (992 mg, 7.18 mmol, 1.5 equiv) in isopropanol (28 mL). The resulting solution was stirred overnight at 110° C. in an oil bath. The resulting mixture was concentrated under vacuum and the residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> (150 mL). The solids were filtered out and the filtrate was concentrated under vacuum. The residue was purified by C18 chromatography (MeCN/H<sub>2</sub>O+0.05% TFA, 1:4) to afford the title compound as a yellow solid (0.8 g, 72% yield). MS: (ES, m/z): 234 [M+H]<sup>+</sup>.

Step-3: Methyl 4-methyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxylate



Into a 25-mL round-bottom flask, was placed methyl 4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxylate (130 mg, 0.56 mmol, 1 equiv), acetic acid (3 mL), acetal (147 g, 3.35 mmol, 6 equiv). The resulting solution was stirred for 2 h at room temperature. Then NaBH(OAc)<sub>3</sub> (1.18 g, 5.58 mmol, 10 equiv) was added. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:5) to afford the title compound as a white solid (18.3 mg, 13% yield). MS: (ES, m/z): 248 [M+H]<sup>+</sup>.

Step-4: N-Hydroxy-4-methyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxamide



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Into a 25-mL round-bottom flask, was placed methyl 4-methyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxylate (18.3 mg, 0.07 mmol, 1 equiv), THF/MeOH (4:1, 1.5 mL), NH<sub>2</sub>OH (50% in water 489 mg, 7.41 mmol, 105 equiv), aq. 1N NaOH (0.15 mL, 2.14 equiv). The resulting solution was stirred for 2.5 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Detector: UV 254, 220 nm) to afford the title compound as a pink solid (8.9 mg, 42% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.34 (br s, 1H), 9.38-8.98 (br s, 1H), 7.69-7.47 (m, 3H), 4.73-4.59 (m, 2H), 4.39-4.22 (m, 1H), 3.73-3.69 (m, 1H), 2.63 (s, 3H), 1.69-1.62 (m, 1H), 1.43-1.32 (m, 1H), 1.29-1.17 (m, 1H), 1.04-0.94 (m, 1H). MS: (ES, m/z): 249 [M+H]<sup>+</sup>.

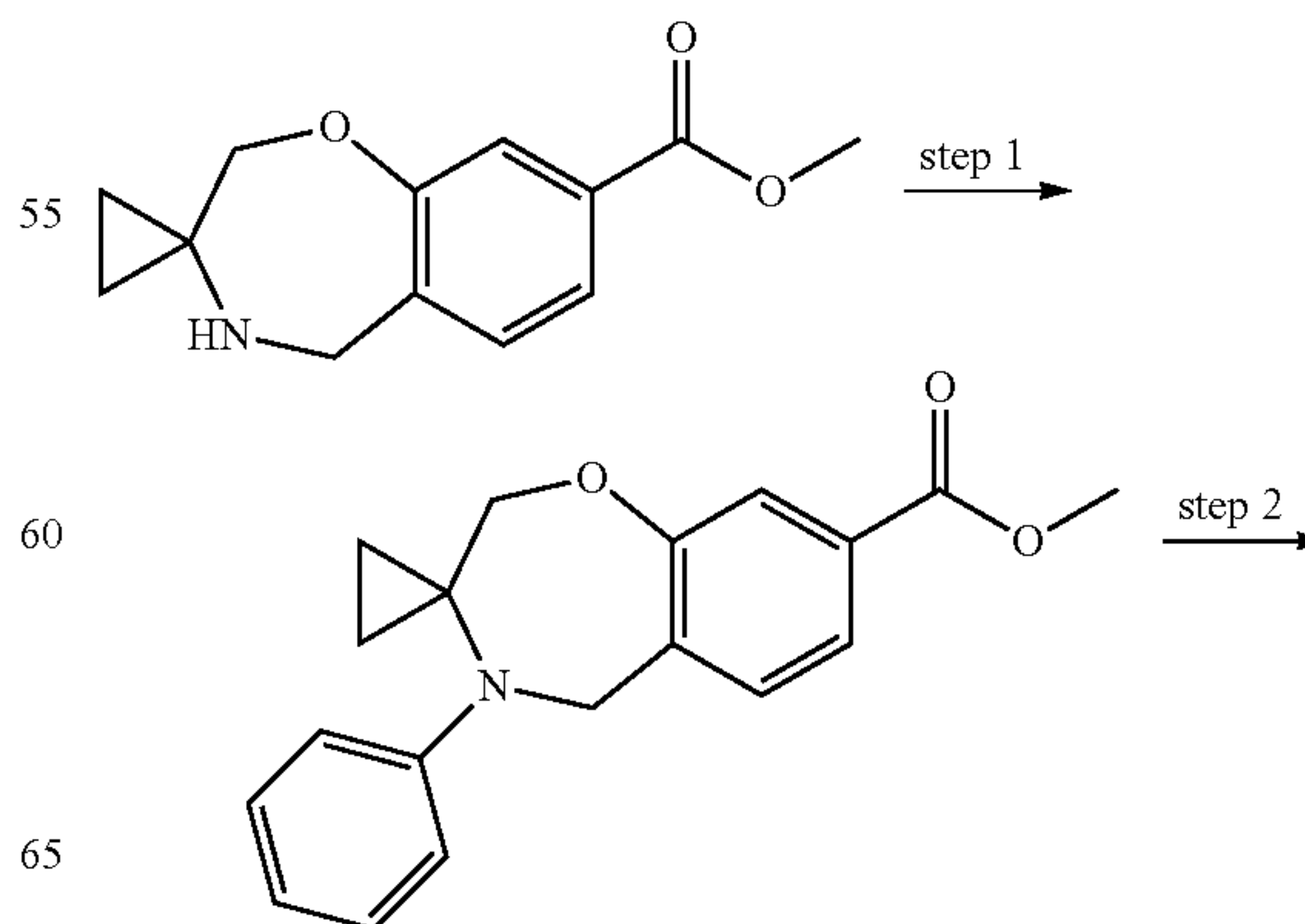
TABLE 25

The following compound was prepared according to the method of Example 51.

Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO- d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 11.31 (br s, 2H), 355 7.51-7.33 (m, [M + H] <sup>+</sup> 5H), 6.92 (d, J = 8.4 Hz, 2H), 4.90-4.17 (m, 4H), 3.77 (m, 5H), 0.82 (s, 4H)	

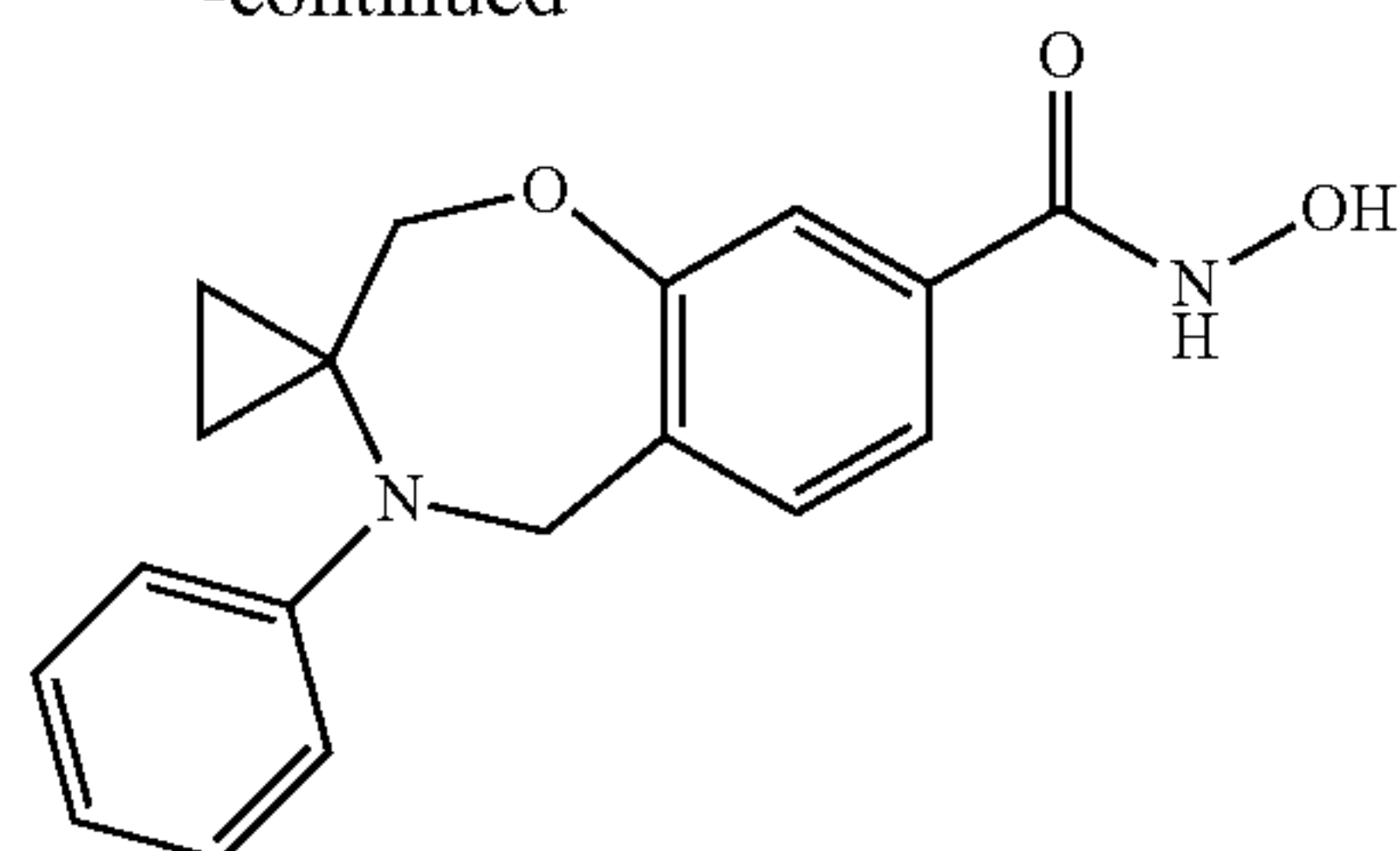
## Example 52

Preparation of N-hydroxy-4-phenyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxamide

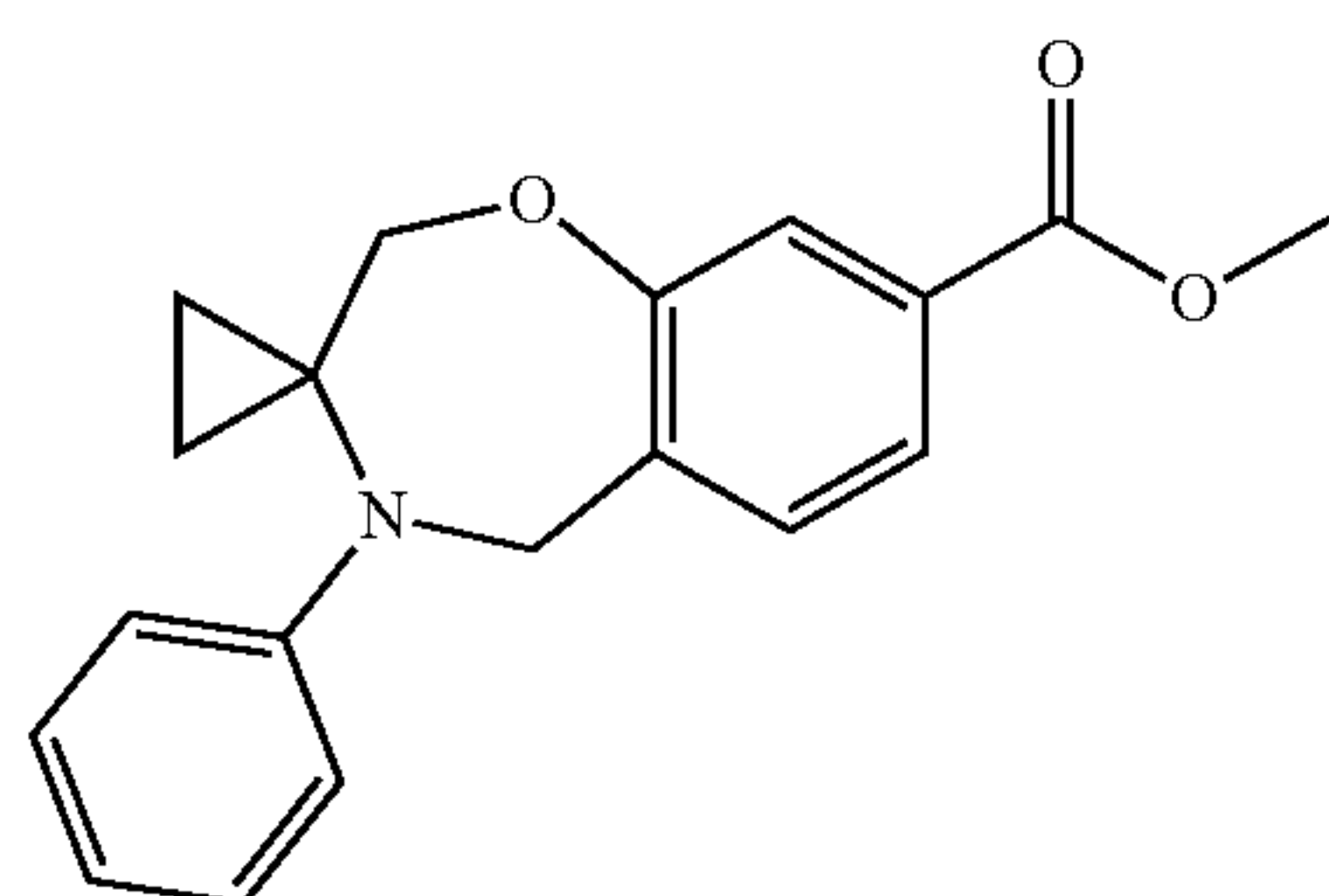


**153**

-continued

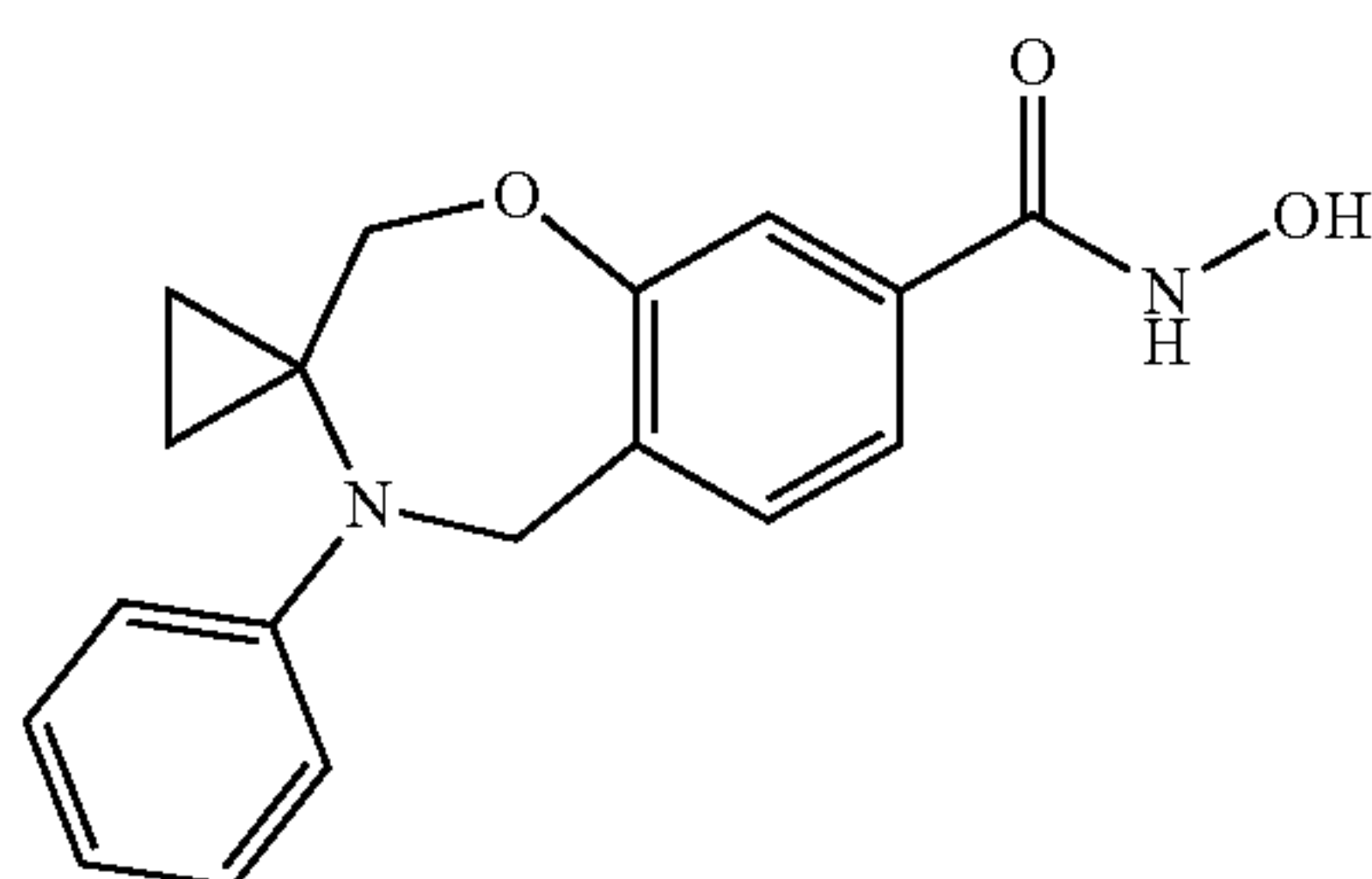


Step-1: Methyl 4-phenyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxylate



Into a 50-mL round-bottom flask, was placed  $\text{Cu}(\text{OAc})_2$  (100 mg, 0.55 mmol, 2.14 equiv), methyl 4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxylate (60 mg, 0.26 mmol, 1 equiv), phenyl boronic acid (65 mg, 0.53 mmol, 2.05 equiv), 4 Å molecular sieves (50 mg),  $\text{CH}_2\text{Cl}_2$  (15 mL),  $\text{Et}_3\text{N}$  (100 mg, 0.99 mmol, 3.84 equiv). The resulting solution was stirred for 48 h at 25° C. The resulting mixture was concentrated under vacuum and then purified by silica gel chromatography ( $\text{EtOAc}$ /pet. ether, 1:1) to afford the title compound as a yellow solid (31 mg, 39% yield). MS: (ES,  $m/z$ ): 310  $[\text{M}+\text{H}]^+$ .

Step-2: N-Hydroxy-4-phenyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxamide



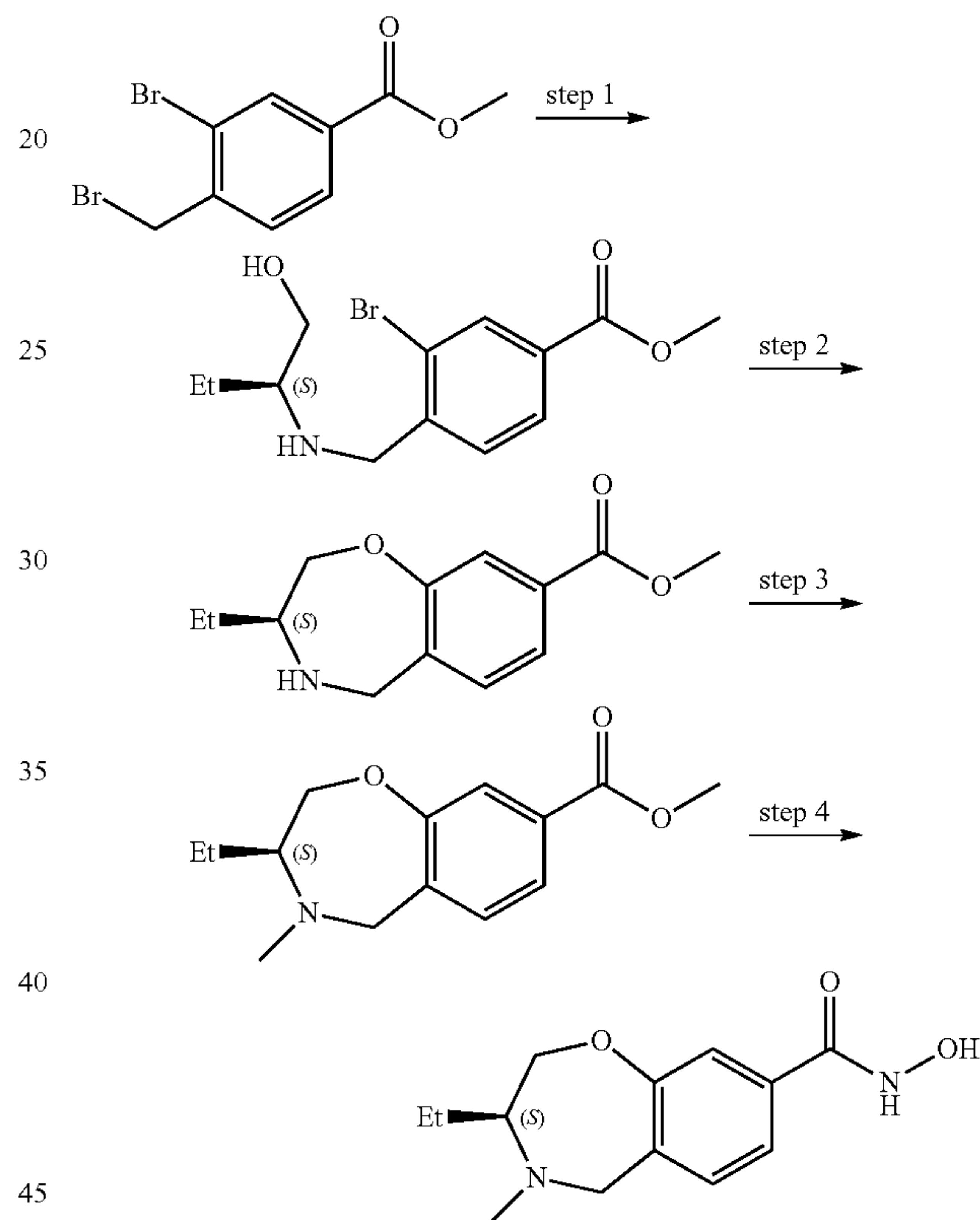
Into a 25-mL round-bottom flask, was placed methyl 4-phenyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxylate (25 mg, 0.08 mmol, 1 equiv),  $\text{NH}_2\text{OH}$  (50% in water, 0.32 g, 4.8 mmol, 60 equiv), aq. 1N NaOH (0.16 mL, 2 equiv), THF/MeOH (4:1, 2 mL). The resulting solution was stirred for 5 h at 25° C. The crude product was purified by Prep-HPLC. (Column: Xbridge Prep C18 OBD, 5  $\mu\text{m}$ , 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 20

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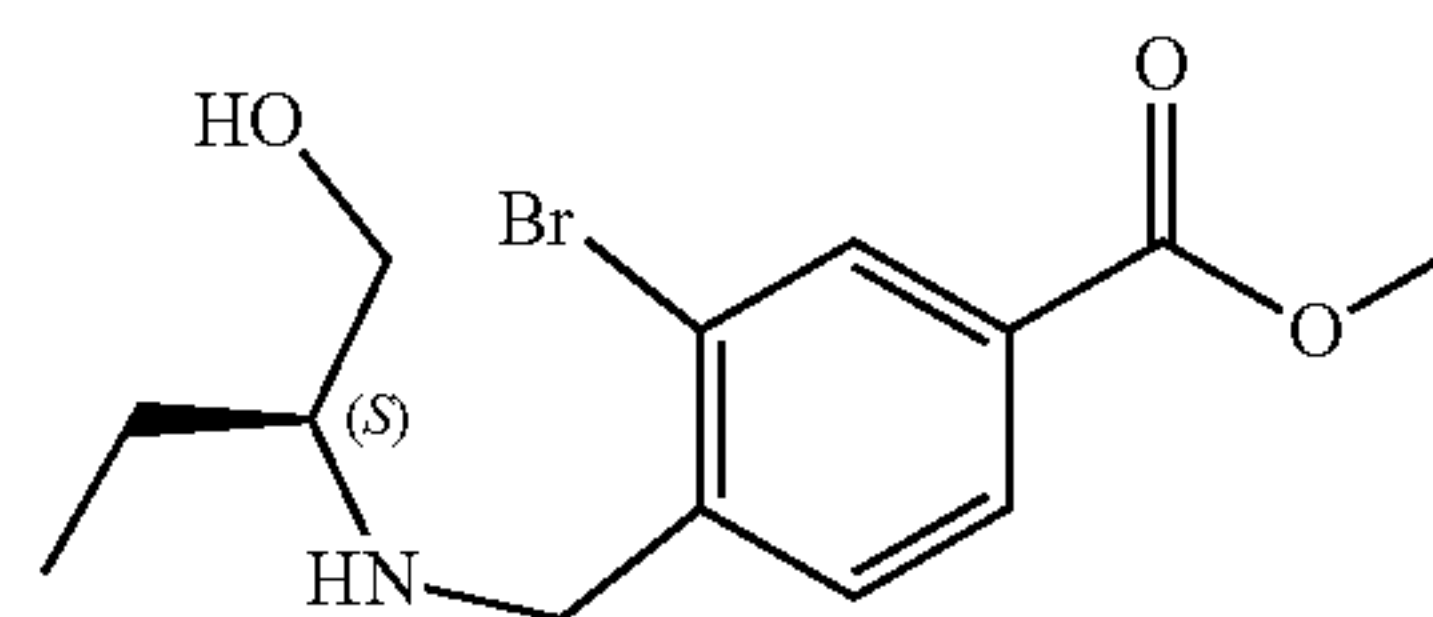
mL/min; Gradient: 30% B to 70% B in 10 min; Detector: UV 254, 220 nm) to afford the title compound as a brown oil (3.1 mg, 12% yield).  $^1\text{H}$ -NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.13 (br s, 1H), 7.61 (d,  $J=2$  Hz, 2H), 7.51-7.26 (m, 2H), 7.14-7.03 (m, 4H), 6.64-6.61 (m, 1H), 5.07 (s, 2H), 4.42 (s, 2H), 1.23-1.16 (m, 2H), 0.99-0.85 (m, 2H). MS: (ES,  $m/z$ ): 311  $[\text{M}+\text{H}]^+$ .

## Example 53

Preparation of (S)-3-ethyl-N-hydroxy-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Step-: Methyl (S)-3-bromo-4-(((1-hydroxybutan-2-yl)amino)methyl)benzoate



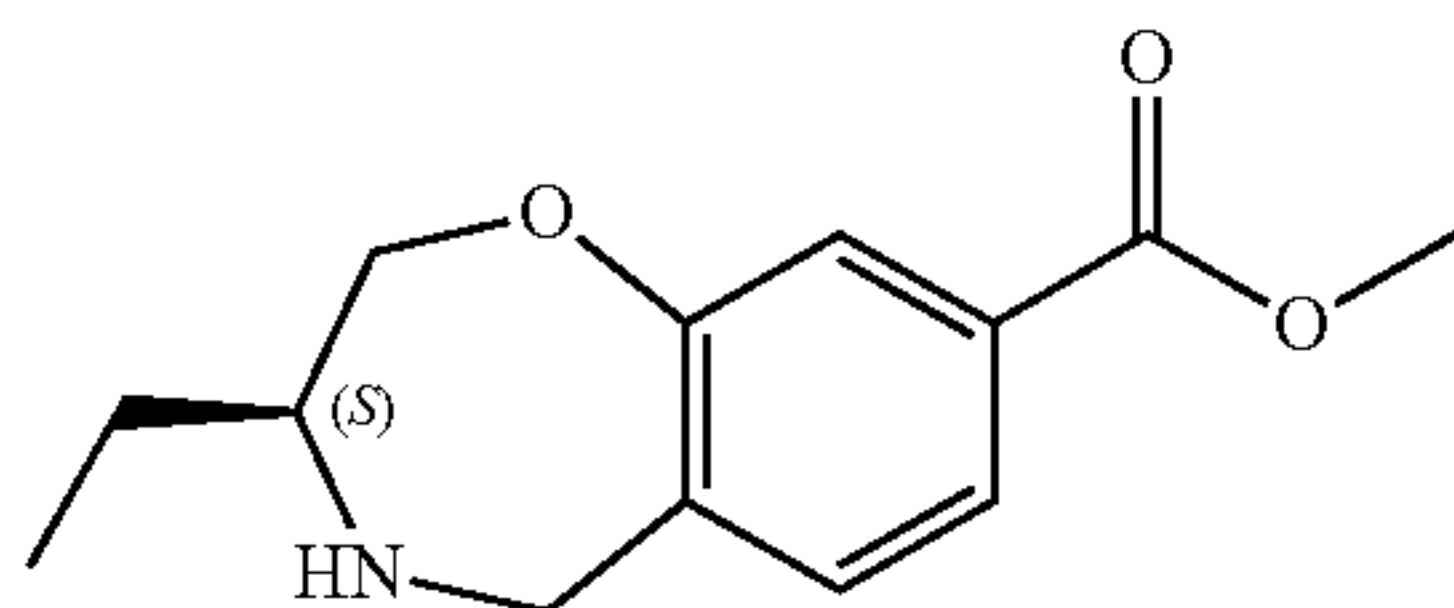
Into a 500-mL round-bottom flask, was placed a solution of (2S)-2-aminobutan-1-ol (7 g, 78.53 mmol, 1.8 equiv) in MeCN (150 mL),  $\text{K}_2\text{CO}_3$  (9 g, 65.22 mmol, 1.5 equiv) and a solution of methyl 3-bromo-4-(bromomethyl)benzoate (13.5 g, 43.84 mmol, 1 equiv) in MeCN (100 mL). The resulting mixture was stirred for 14 h at room temperature and then concentrated under vacuum. The residue was



**155**

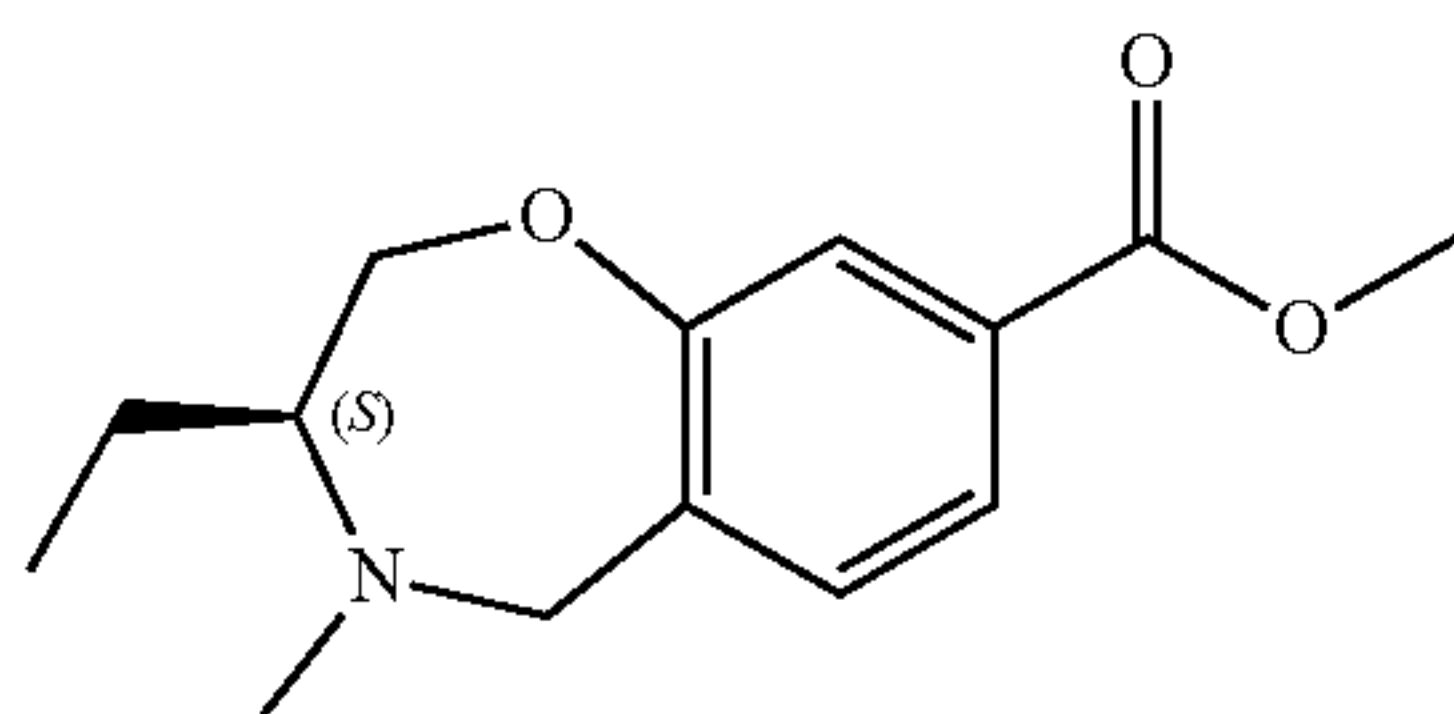
diluted with H<sub>2</sub>O (200 mL) and extracted with EtOAc (2×200 mL). The combined organic layers were washed with H<sub>2</sub>O (2×200 mL) and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:9) to afford the title compound as an off-white solid (6.9 g, 50% yield). MS: (ES, m/z): 316 [M+H]<sup>+</sup>.

Step-2: Methyl (S)-3-ethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 150-mL pressure tank reactor purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl (S)-3-bromo-4-(((1-hydroxybutan-2-yl)amino)methyl)benzoate (6.9 g, 21.82 mmol, 1 equiv) in isopropanol (130 mL), K<sub>2</sub>CO<sub>3</sub> (5.14 g, 37.25 mmol, 1.7 equiv) and CuI (2.08 g, 10.95 mmol, 0.5 equiv). The resulting mixture was stirred for 20 h at 110° C. in an oil bath, then was concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (1 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×100 mL). The combined organic layers were washed with H<sub>2</sub>O (3×100 mL) and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a green oil (2.1 g), which was used without further purification. MS: (ES, m/z): 236 [M+H]<sup>+</sup>.

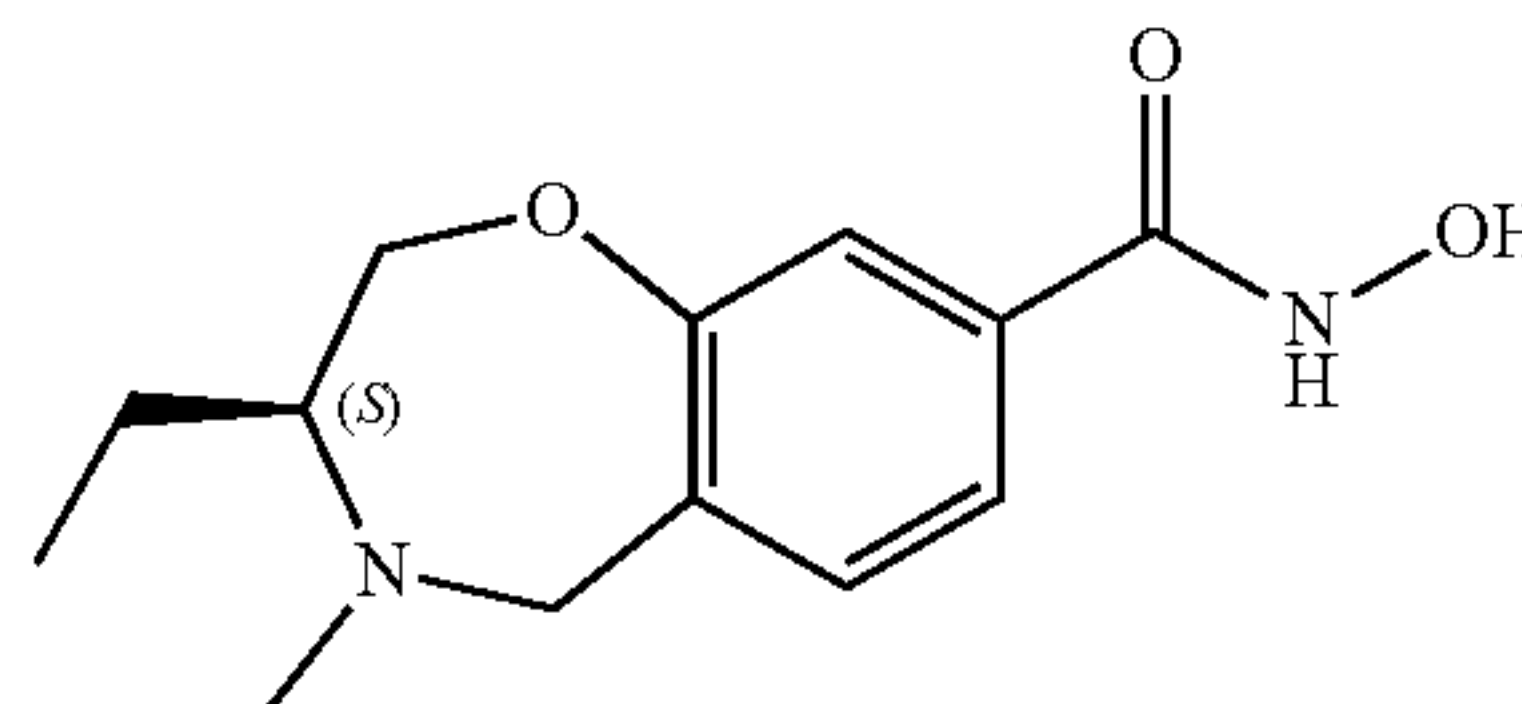
Step-3: Methyl (S)-3-ethyl-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed a solution of methyl (S)-3-ethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (130 mg, 0.55 mmol, 1 equiv) in acetic acid (3 mL). This was followed by the addition of formaldehyde (100 mg, 3.33 mmol, 6 equiv) and the reaction was stirred for 2 h. To this was added NaBH(OAc)<sub>3</sub> (1.16 g, 5.50 mmol, 10 equiv). The resulting solution was stirred for 26 h at room temperature and concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (10 mL), extracted with EtOAc (3×10 mL). The organic combined layers were concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a colorless oil (79 mg, 57% yield). MS: (ES, m/z): 250 [M+H]<sup>+</sup>.

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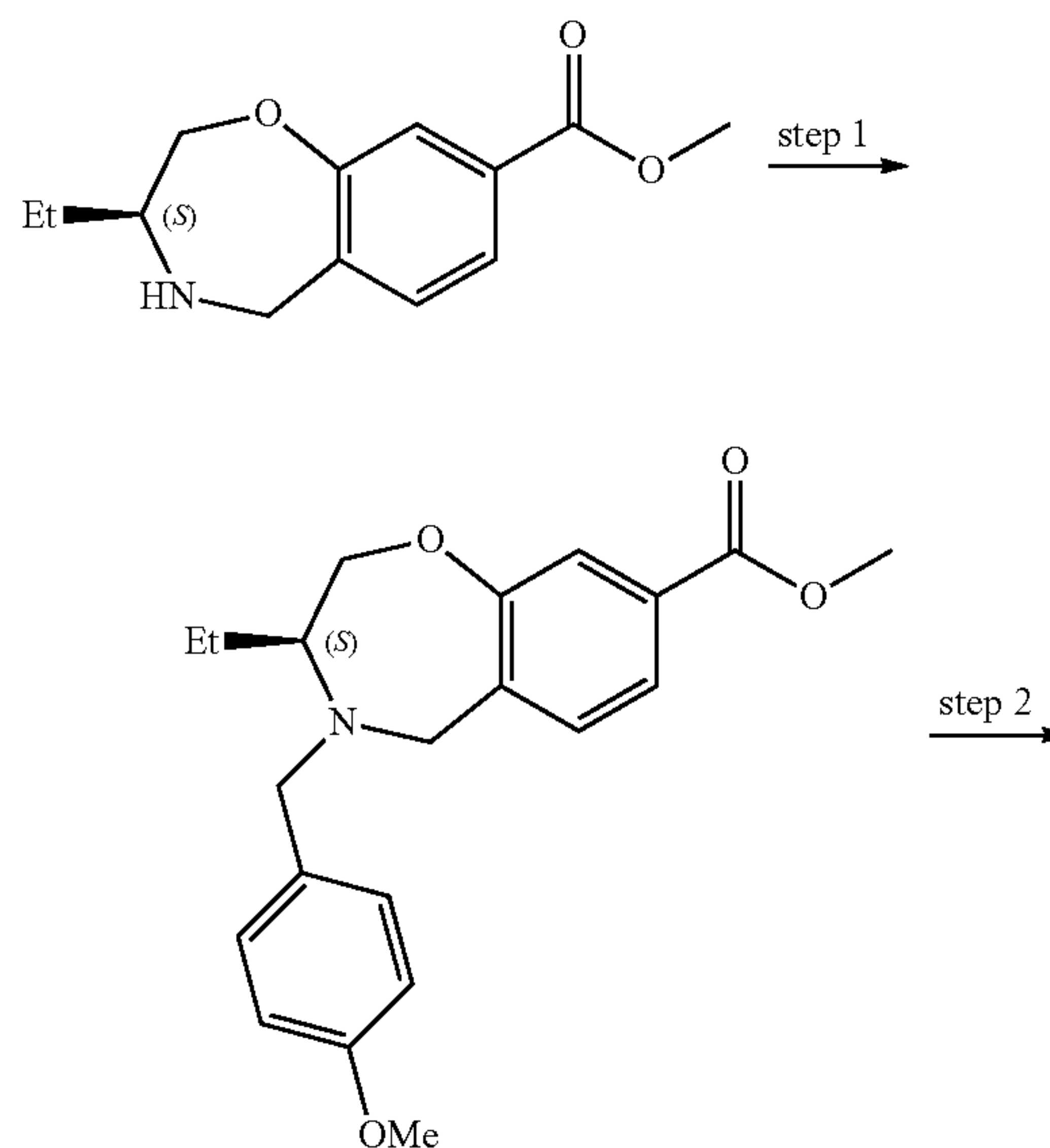
Step-4: (S)-3-Ethyl-N-hydroxy-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed a solution of methyl (S)-3-ethyl-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (79 mg, 0.32 mmol, 1 equiv) in THF:MeOH (4:1, 2 mL). This was followed by the addition of NH<sub>2</sub>OH (50% in H<sub>2</sub>O, 0.63 mL, 30 equiv) and aq. 1N NaOH (0.64 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×250 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 30 mL/min; Gradient: 15% B to 40% B in 7 min; Detector: UV 254, 220 nm). Aq. 1N HCl (0.32 mL) was added to the product fractions and lyophilized to afford the title compound as the HCl salt as a light brown solid (13.9 mg, 15% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.60 (s, 1H), 11.59-11.21 (m, 1H), 7.58-7.42 (m, 3H), 4.78-4.77 (d, J=4.0 Hz, 0.6H), 4.71-4.67 (d, J=16.0 Hz, 0.6H), 4.39-4.32 (m, 2.7H), 4.10-4.06 (m, 0.5H), 3.77 (m, 0.5H), 3.47-3.46 (m, 0.5H), 2.76-2.75 (m, 1.5H), 2.67-2.51 (m, 1.5H), 2.08-2.00 (m, 1H), 1.83-1.80 (m, 0.5H), 1.58-1.56 (m, 0.5H), 1.05-1.01 (m, 3H). MS: (ES, m/z): 251 [M+H]<sup>+</sup>.

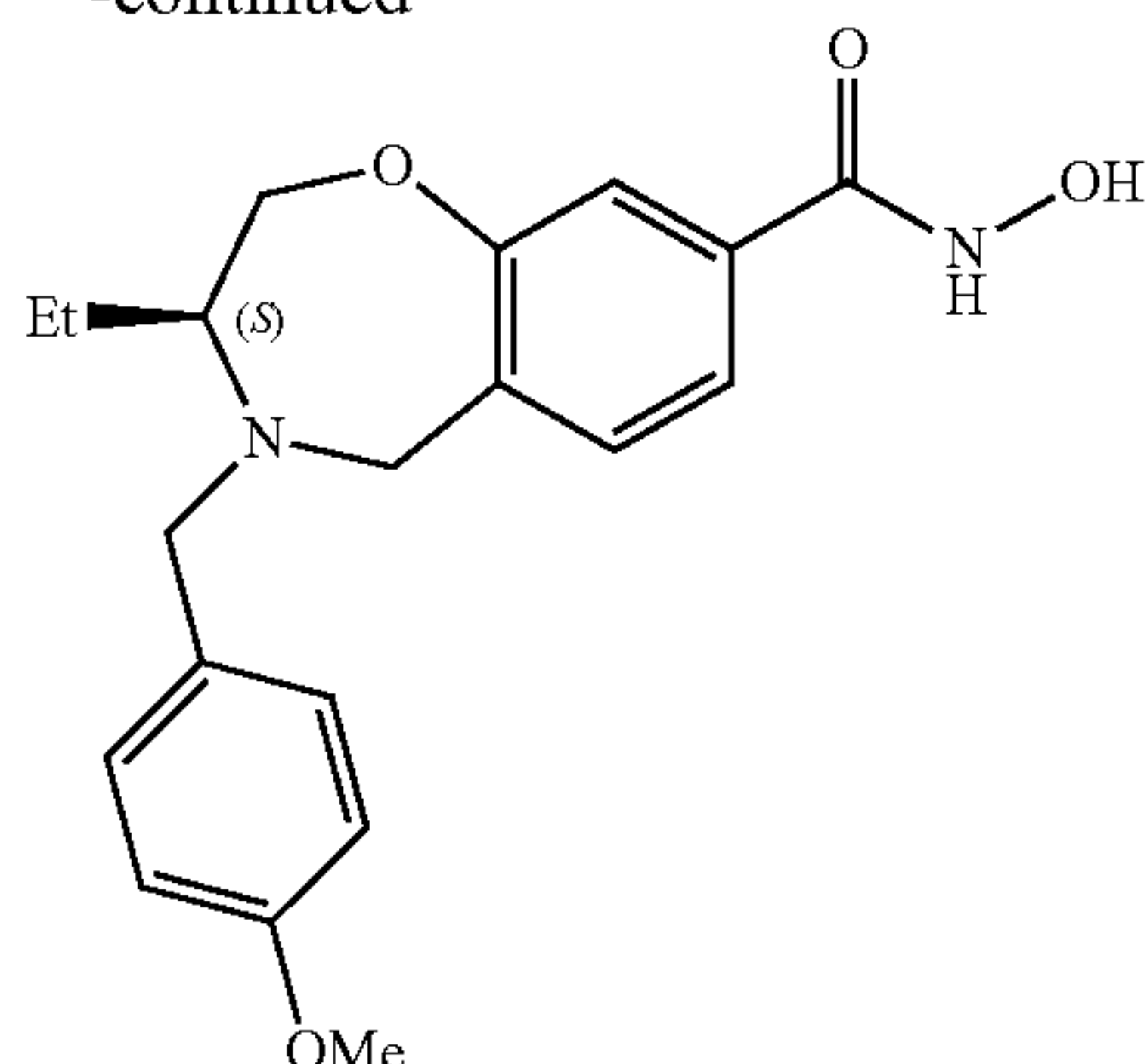
## Example 54

Preparation of (S)-3-ethyl-N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

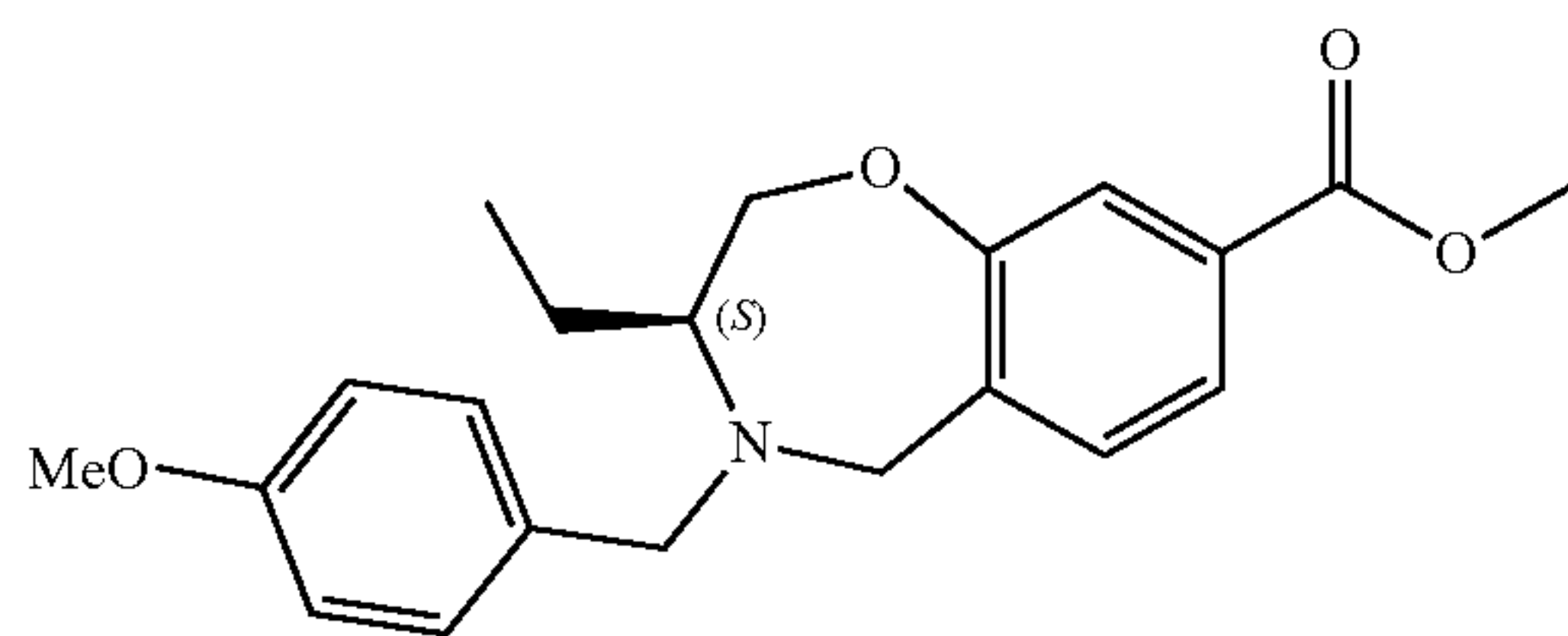


**157**

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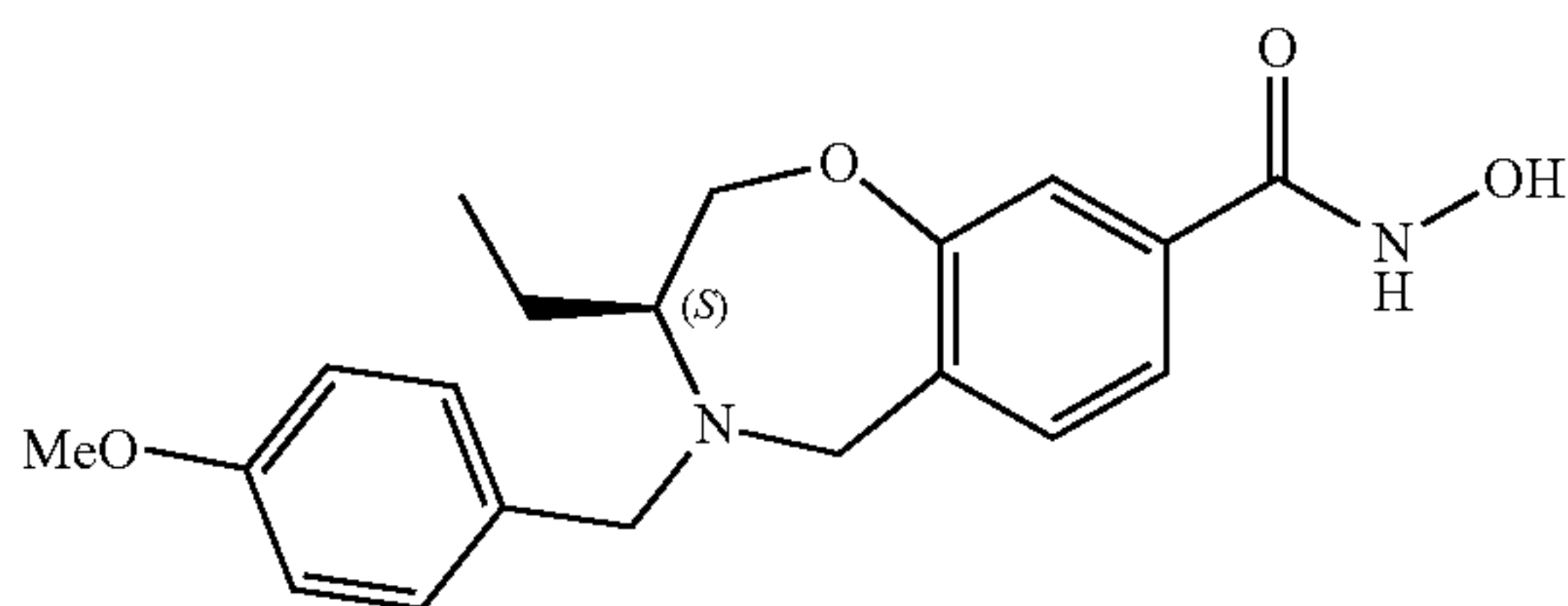


Step-1: Methyl (S)-3-ethyl-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed a solution of methyl (S)-3-ethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (130 mg, 0.55 mmol, 1 equiv) in THF (2 mL). This was followed by the addition of sodium hydride (60% dispersion in oil, 68 mg, 3 equiv) at 0° C. in 30 min. To this was added 1-(bromomethyl)-4-methoxybenzene (111 mg, 0.55 mmol, 1 equiv). The resulting solution was stirred for 20 h at room temperature. The reaction was then quenched by the addition of aq. NH<sub>4</sub>Cl solution (3 mL), then concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (10 mL), extracted with EtOAc (3×10 mL), and the combined organic layers were concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:4) to afford the title compound as a yellow oil (140 mg). MS: (ES, m/z): 356 [M+H]<sup>+</sup>.

Step-2: (S)-3-Ethyl-N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



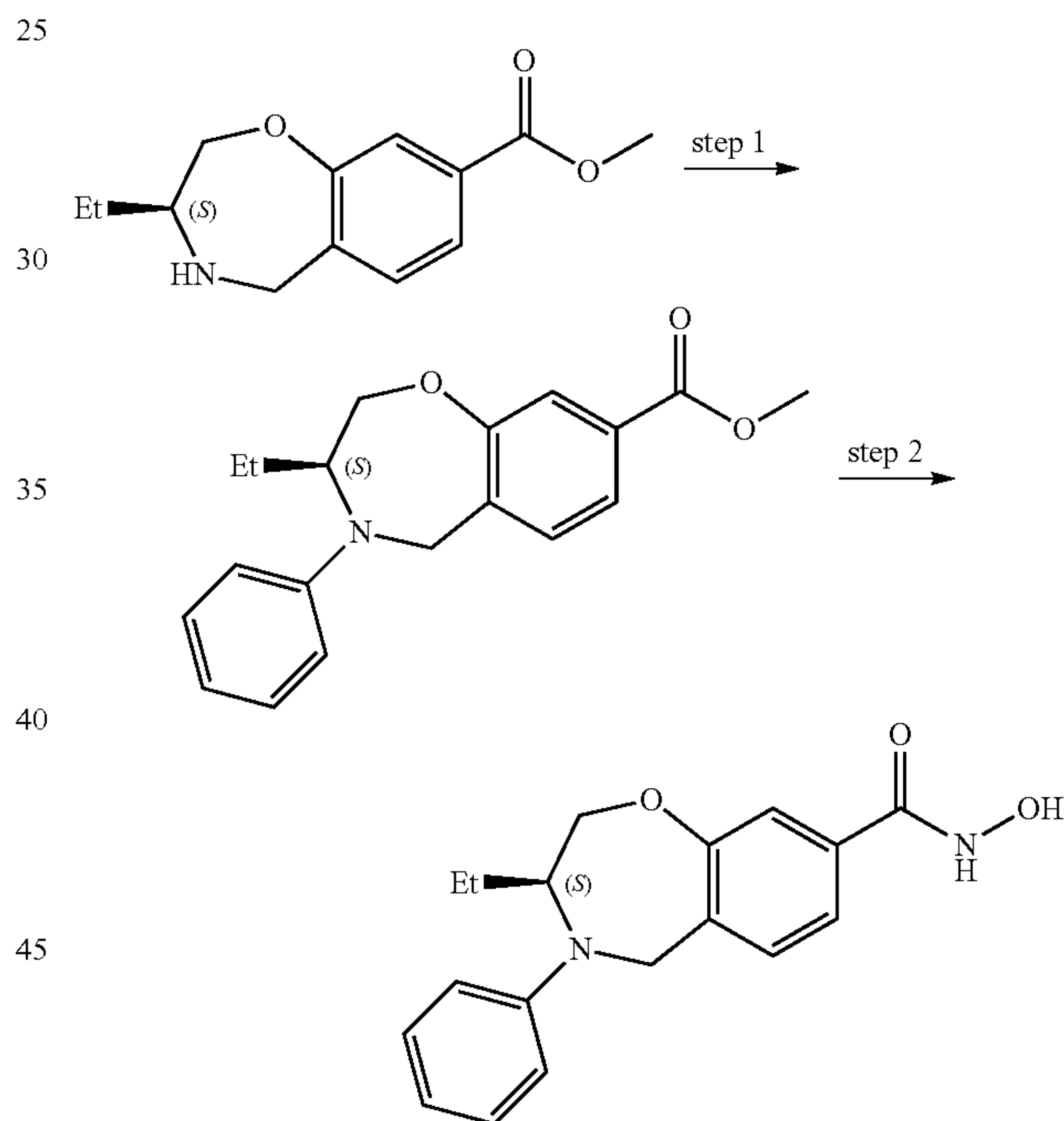
Into a 8-mL vial, was placed a solution of methyl (S)-3-ethyl-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (140 mg, 0.39 mmol, 1 equiv) in THF:MeOH (4:1, 2 mL). This was followed by the addition of NH<sub>2</sub>OH (50% in H<sub>2</sub>O, 0.79 mL, 30 equiv) and aq. 1N

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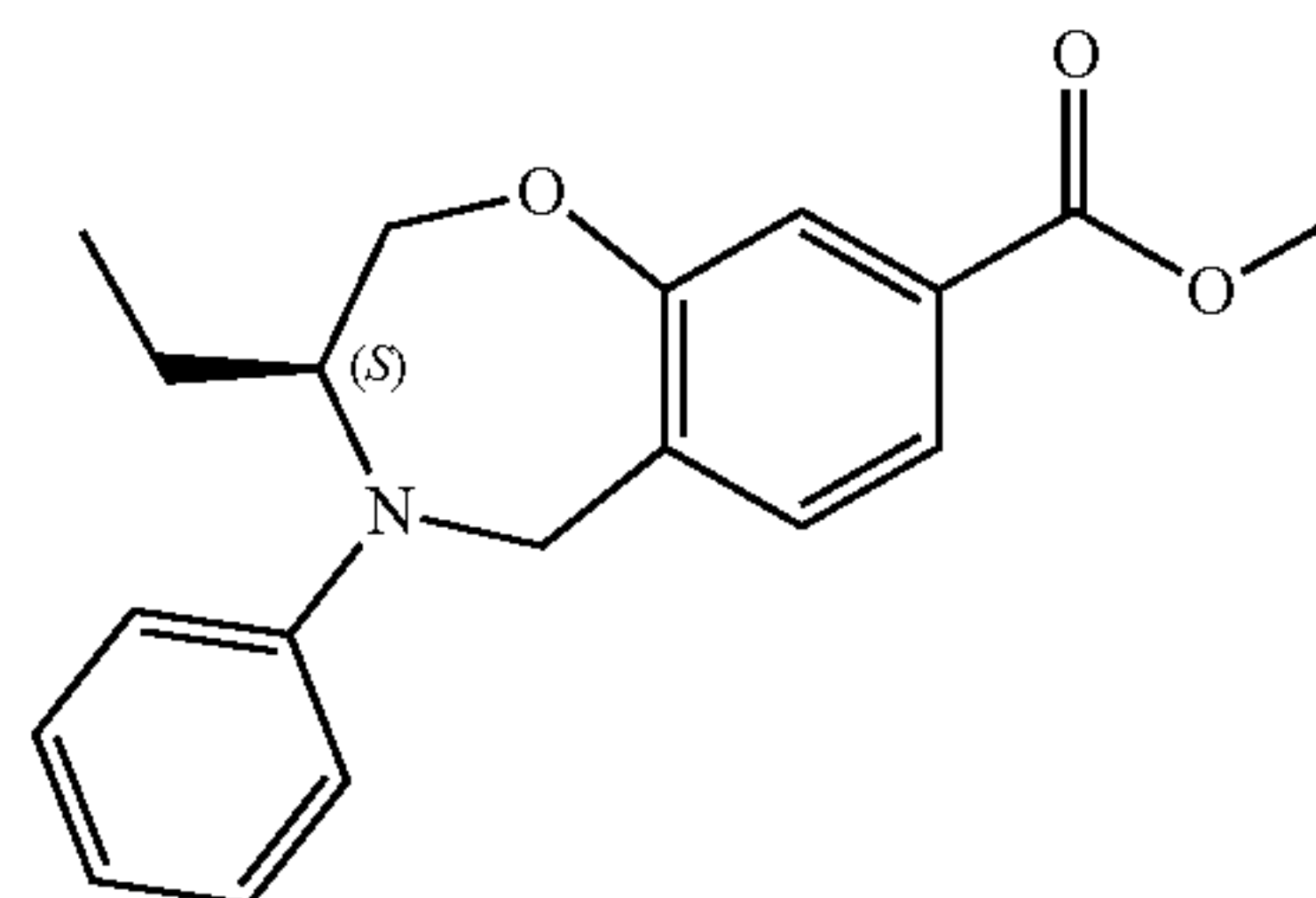
NaOH (0.79 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×250 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 30 mL/min; Gradient: 30% B to 70% B in 10 min; Detector: UV 254, 220 nm). Aq. 1N HCl (0.4 mL) was added to the product fractions and lyophilized to afford the title compound as the HCl salt as a pink solid (68.7 mg, 44% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.34 (s, 1H), 11.02-10.74 (m, 1H), 9.19-9.14 (br, 1H), 7.56-7.20 (m, 5H), 7.10-7.02 (m, 2H), 4.80-4.72 (d, J=32 Hz, 0.71H), 4.60-4.52 (m, J=32 Hz, 0.76H), 4.51-4.19 (m, 5H), 3.88 (m, 3H), 3.50-3.31 (m, 1H), 2.08-1.91 (m, 2H), 1.01-0.92 (m, 3H). MS: (ES, m/z): 357 [M+H]<sup>+</sup>.

## Example 55

Preparation of (S)-3-ethyl-N-hydroxy-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Step-1: Methyl (S)-3-ethyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate





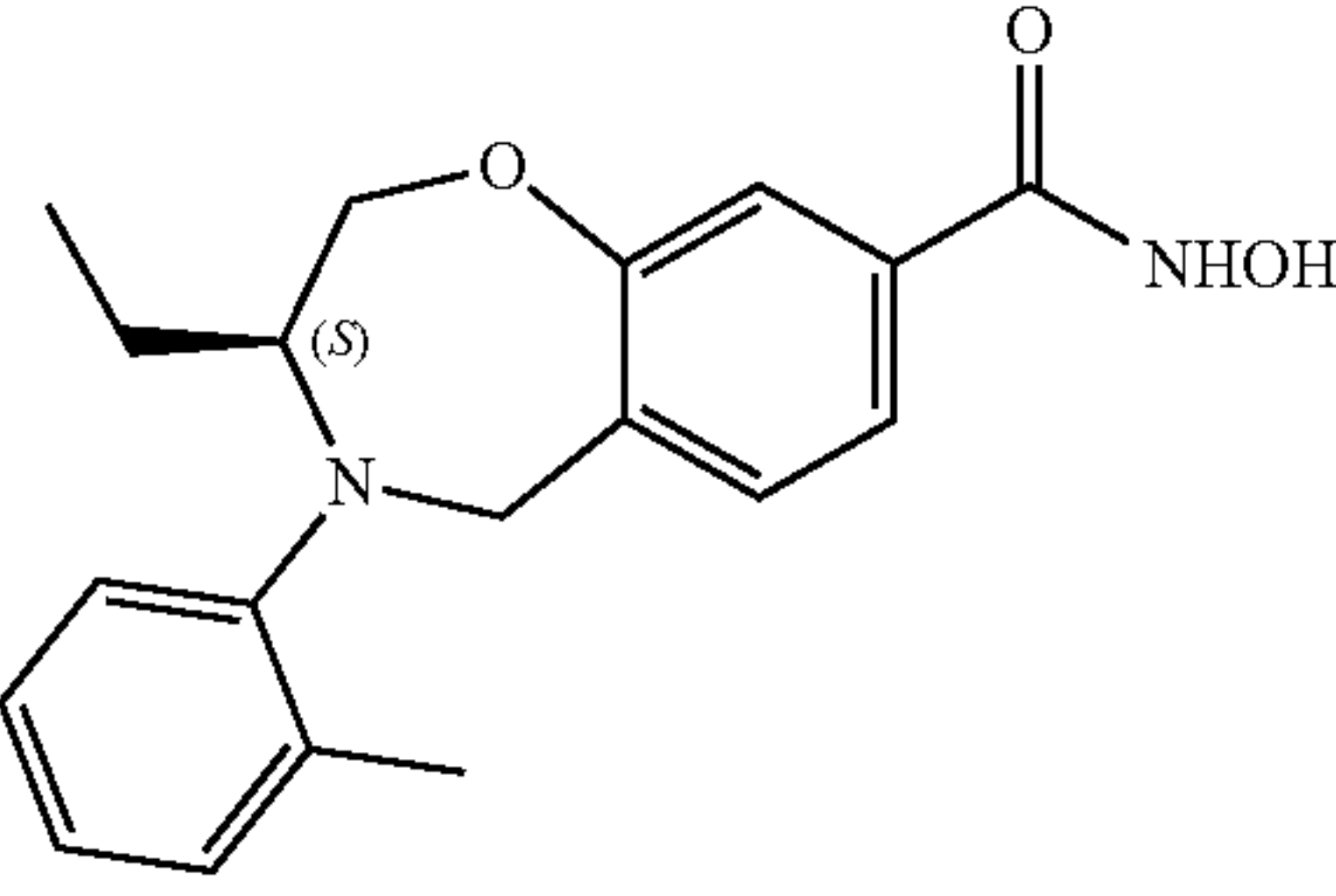
## 159

Into a 8-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl (S)-3-ethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (200 mg, 0.85 mmol, 1 equiv) in

## 160

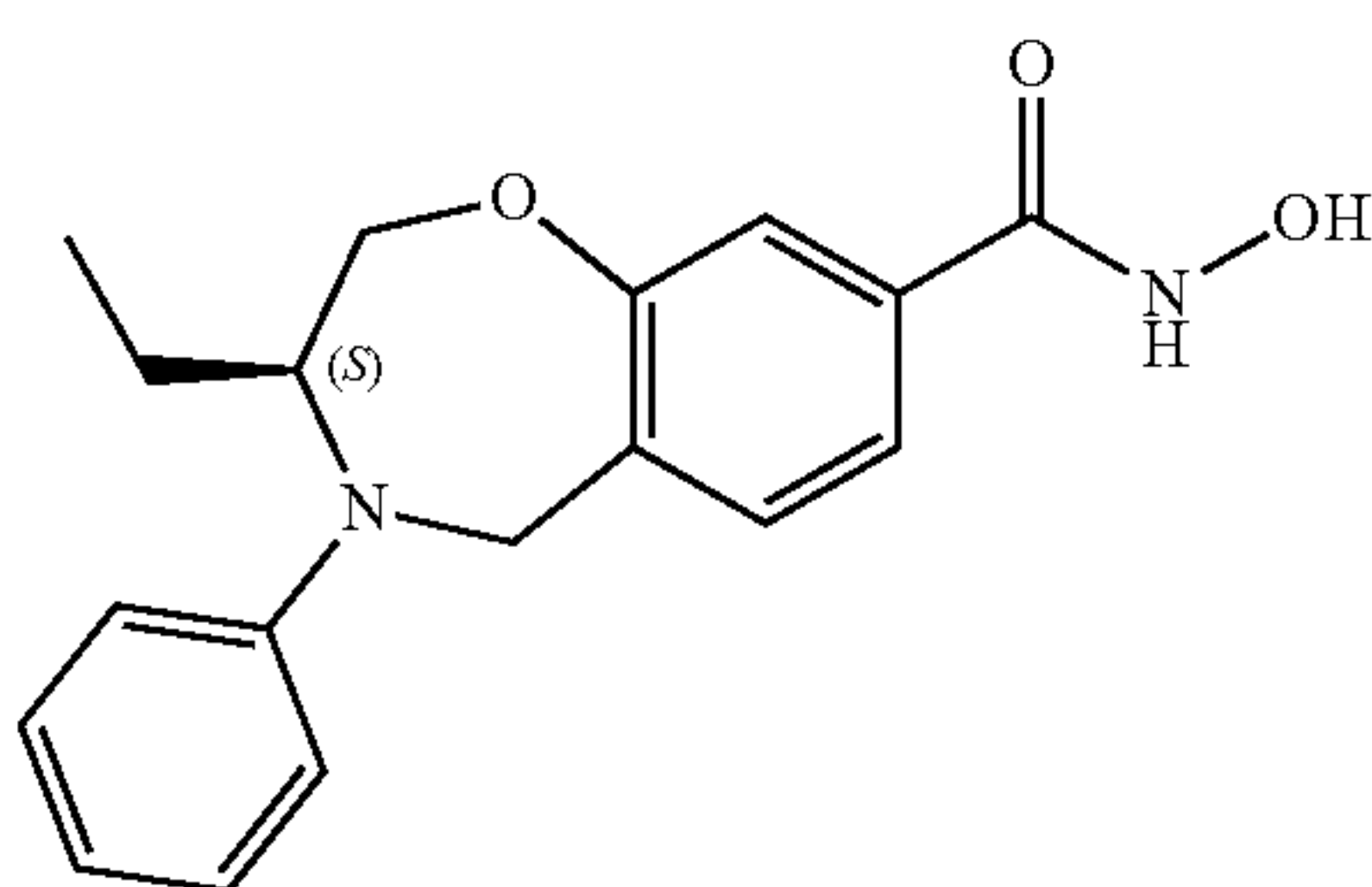
6.69 (d, J=8.0 Hz, 2H), 6.55-6.53 (d, J=8.0 Hz, 1H), 4.95-4.91 (m, 1H), 4.41-4.36 (m, 1H), 4.35-4.29 (m, 2H), 4.13 (m, 1H), 1.67-1.56 (m, 2H), 1.01-0.98 (m, 3H). MS: (ES, m/z): 313 [M+H]<sup>+</sup>.

TABLE 26

The following compound was prepared according to the method of Example 55, using 1-bromo-2-methylbenzene in Step 1.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 327 [M + H] <sup>+</sup>	11.10 (br, 1H), 7.26-7.23 (m, 2H), 7.19-7.17 (m, 1H), 7.09-7.06 (m, 2H), 7.04-7.02 (m, 1H), 6.91-6.89 (m, 1H), 4.55-4.51 (d, J = 16.0 Hz, 1H), 4.38-4.26 (m, 2H), 4.14-4.01 (d, J = 16.0 Hz, 1H), 3.54-3.52 (m, 1H), 2.24 (s, 3H), 1.54-1.41 (m, 2H), 0.88-0.84 (m, 3H)

toluene (2.5 mL), iodobenzene (519 mg, 2.54 mmol, 3 equiv), Cs<sub>2</sub>CO<sub>3</sub> (834 mg, 2.56 mmol, 3 equiv), BINAP (211 mg, 0.34 mmol, 0.4 equiv) and Pd(OAc)<sub>2</sub> (38 mg, 0.17 mmol, 0.2 equiv). The resulting mixture was stirred for 20 h at 110° C. in an oil bath. The resulting mixture was concentrated under vacuum. The residue was diluted with H<sub>2</sub>O (10 mL), extracted with EtOAc (3×10 mL), and the combined organic layers were concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:5) to afford the title compound as a yellow oil (40 mg, 15% yield). MS: (ES, m/z): 312 [M+H]<sup>+</sup>.

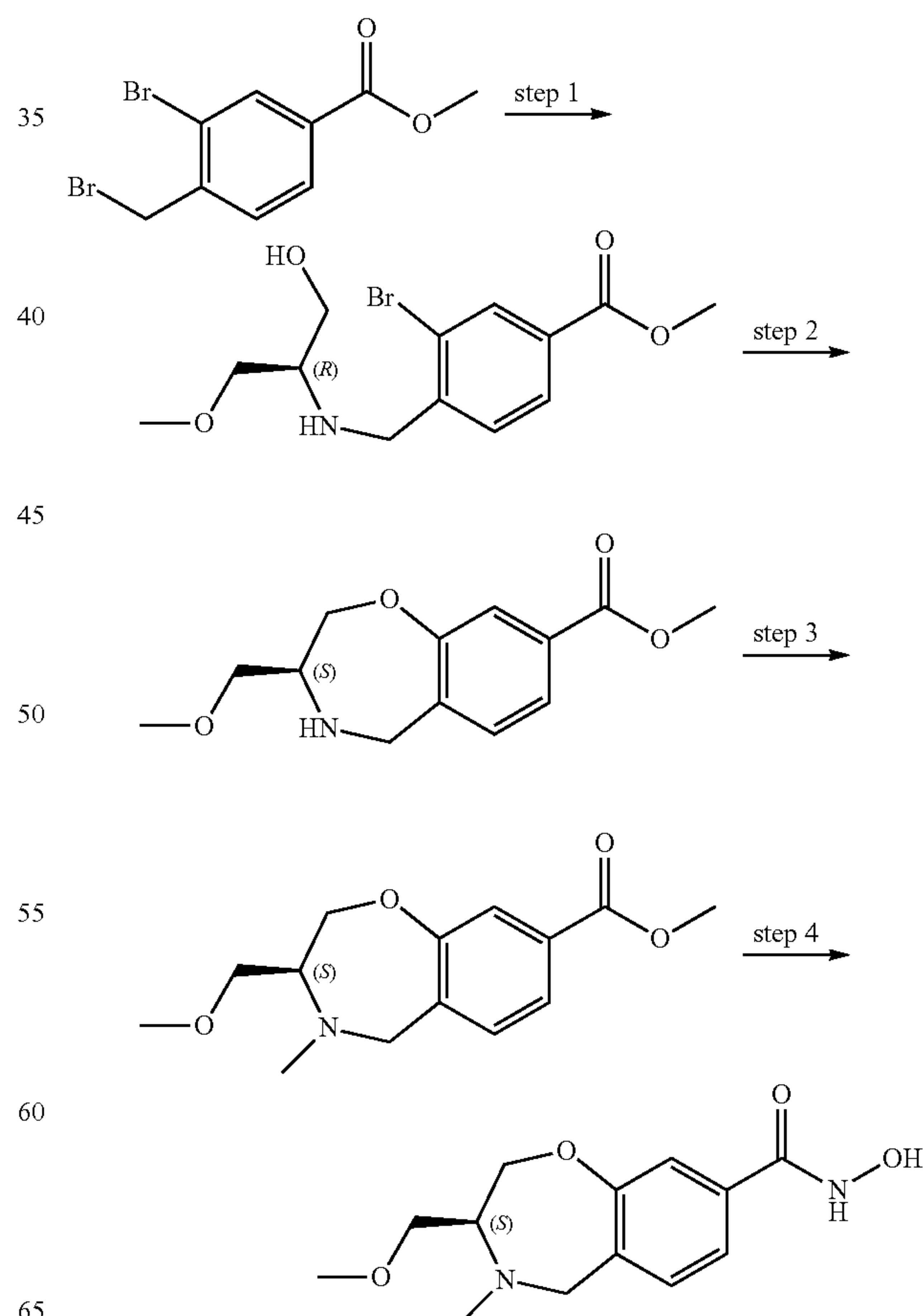
Step-2: (S)-3-Ethyl-N-hydroxy-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 8-mL vial, was placed a solution of methyl (S)-3-ethyl-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (40 mg, 0.13 mmol, 1 equiv) in THF/MeOH (4:1, 1.5 mL). This were followed by the addition of NH<sub>2</sub>OH (50% in H<sub>2</sub>O, 0.26 mL, 30 equiv.) and aq. 1N NaOH (0.26 mL, 2 equiv.). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 30 mL/min; Gradient: 15% B to 60% B in 7 min; Detector: UV 254, 220 nm). Aq. 1N HCl (0.13 mL) was added to the product fractions and lyophilized to afford the title compound as the HCl salt as an off-white solid (12.2 mg, 27% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.01 (s, 1H), 7.49-7.47 (d, J=8.0 Hz, 1H), 7.36-7.34 (d, J=8.0 Hz, 1H), 7.09-7.03 (m, 3H), 6.71-

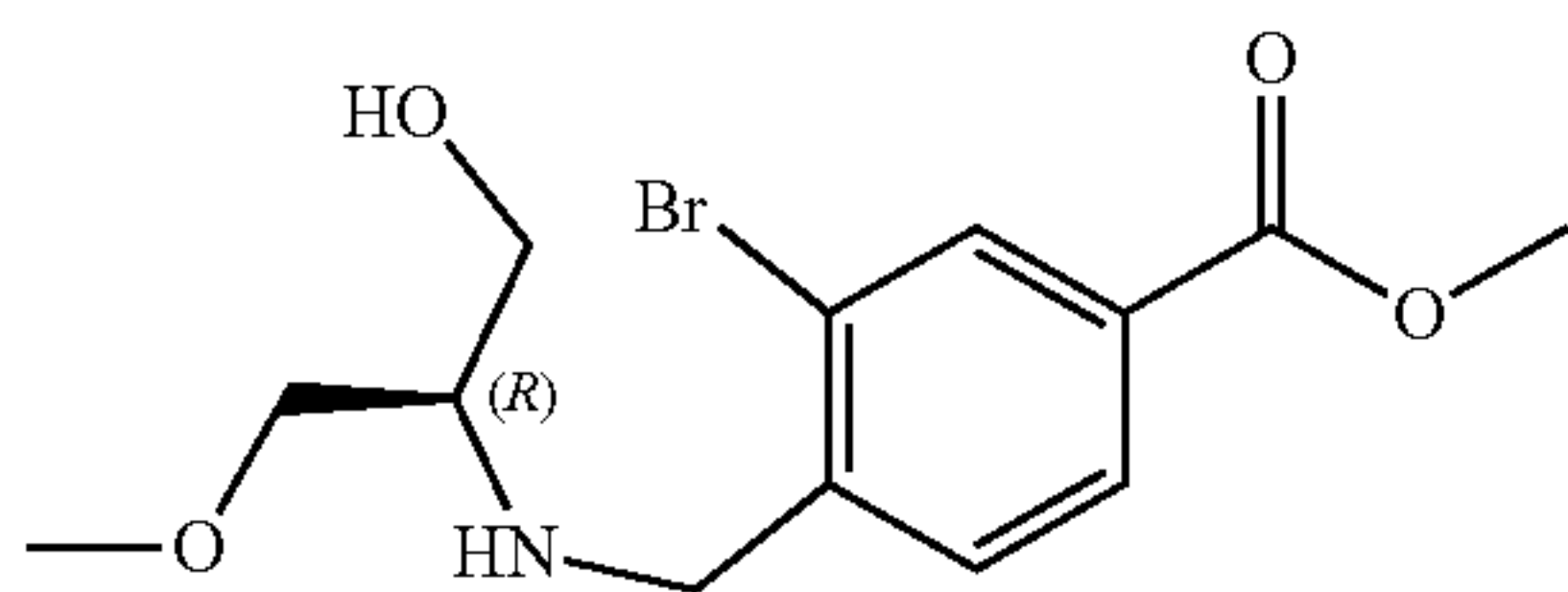
## Example 56

Preparation of (S)-N-hydroxy-3-(methoxymethyl)-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



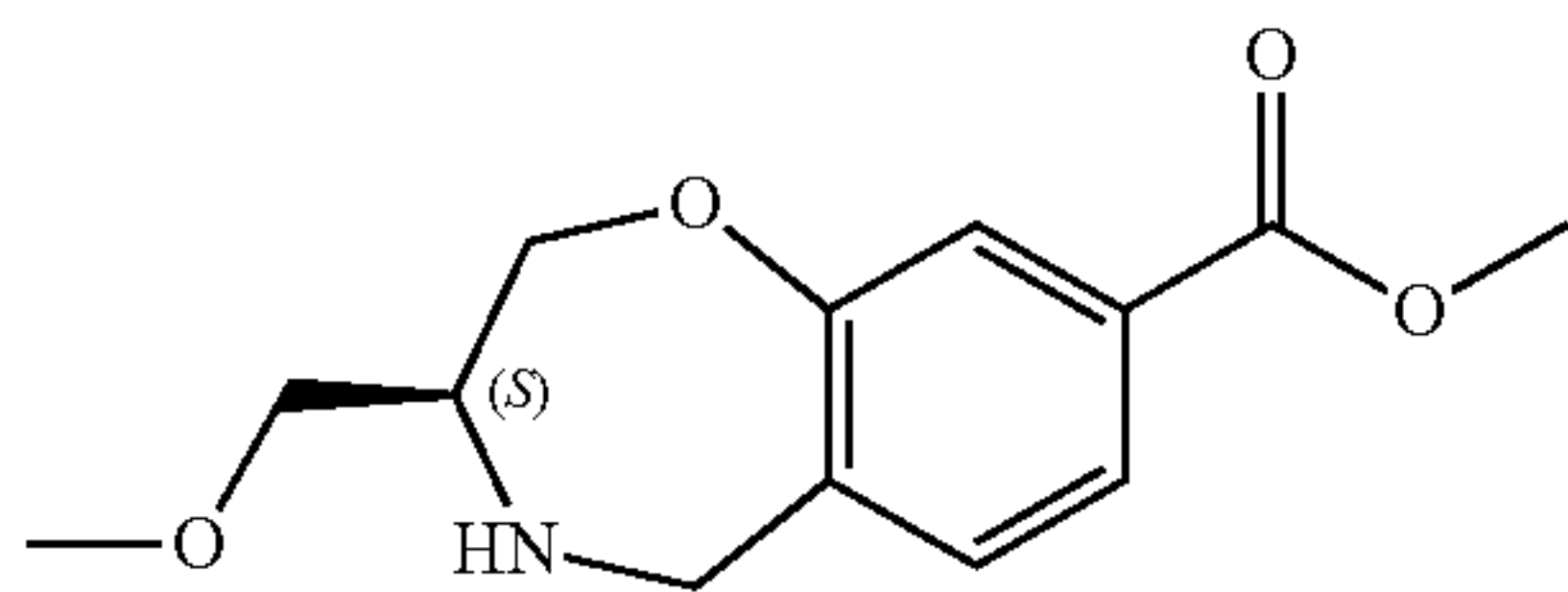
**161**

Step-1: Methyl (R)-3-bromo-4-(((1-hydroxy-3-methoxypropan-2-yl)amino)methyl)benzoate



Into a 500-mL round-bottom flask, was placed (2R)-2-amino-3-methoxypropan-1-ol hydrochloride (6 g, 42.37 mmol, 1.2 equiv), a solution of  $K_2CO_3$  (14 g, 101.3 mmol, 2.8 equiv) in MeCN (100 mL). This was followed by the addition of a solution of methyl 3-bromo-4-(bromomethyl)benzoate (11 g, 35.72 mmol, 1 equiv) in MeCN (100 mL) dropwise with stirring at 0° C. The resulting solution was stirred overnight at room temperature, then concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a yellow solid (4.5 g, 38% yield). MS: (ES, m/z): 332, 334  $[M+H]^+$ .

Step-2: Methyl (S)-3-(methoxymethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



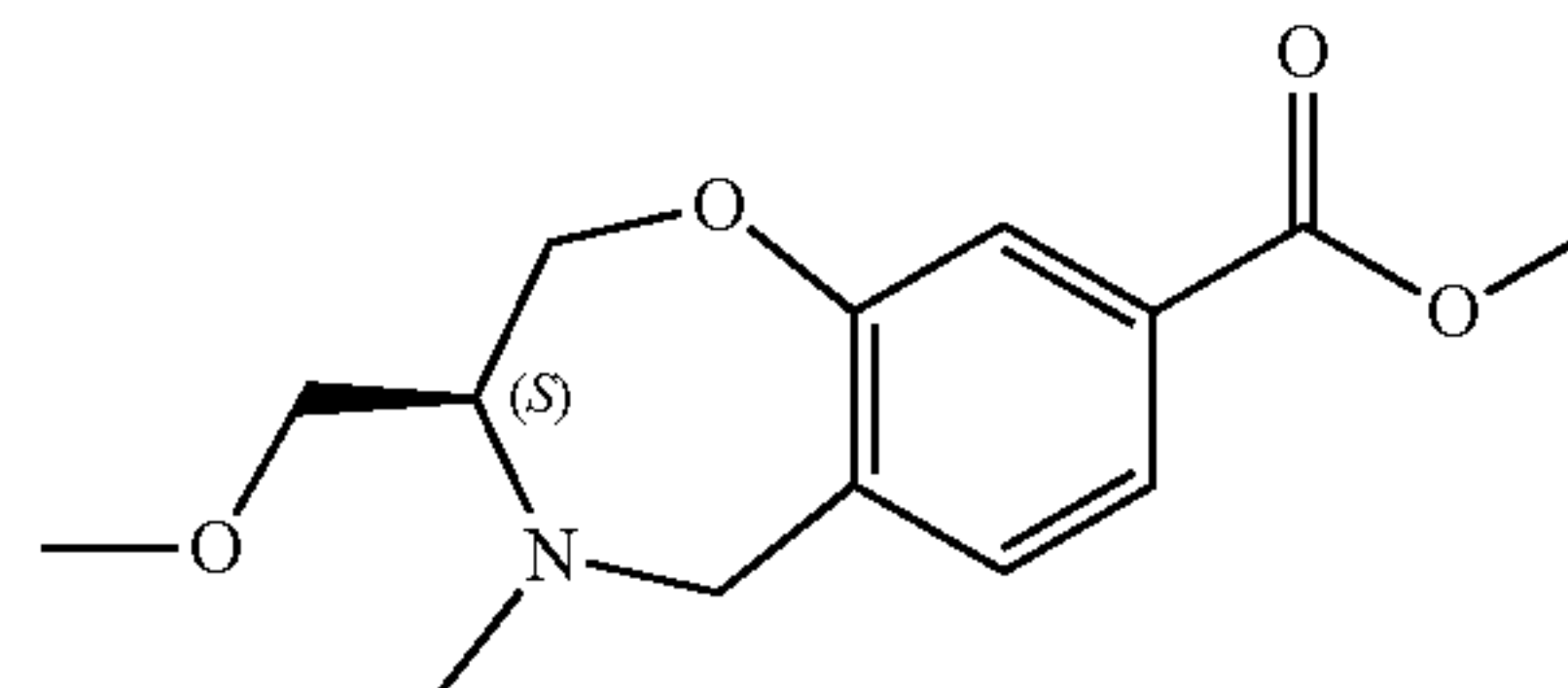
Into a 150-mL sealed tube, was placed a solution of methyl (R)-3-bromo-4-(((1-hydroxy-3-methoxypropan-2-yl)amino)methyl)benzoate (4.5 g, 13.55 mmol, 1 equiv) in isopropanol (120 mL),  $K_2CO_3$  (2.813 g, 20.21 mmol, 1.5 equiv), and CuI (0.76 g, 3.99 mmol, 0.3 equiv). The resulting mixture was stirred overnight at 110° C. in an oil bath, then concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a yellow oil (550 mg, 16% yield). MS: (ES, m/z): 252  $[M+H]^+$ .

**162**

Step-3: Methyl (S)-3-(methoxymethyl)-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

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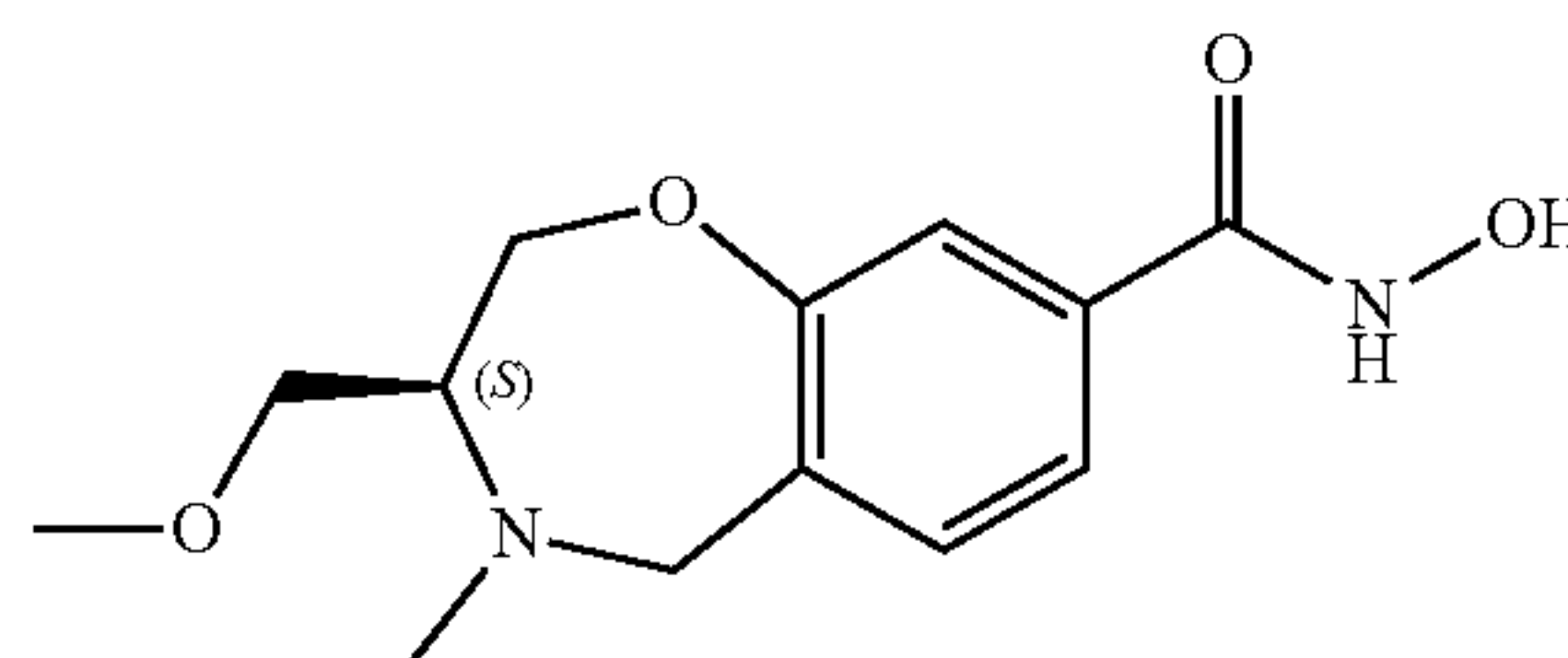
Into a 25-mL round-bottom flask, was placed methyl (S)-3-(methoxymethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (200 mg, 0.80 mmol, 1 equiv), acetic acid (5 mL), acetal (175.2 mg, 4 mmol, 5 equiv). The resulting solution was stirred for 2 h at room temperature. This was followed by the addition of  $NaBH(OAc)_3$  (1182.5 mg, 5.58 mmol, 7 equiv). The resulting mixture was stirred overnight at room temperature. Then the solids were filtered out and the filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a colorless oil (60.2 mg, 29% yield). MS: (ES, m/z): 266  $[M+H]^+$ .

Step-4: (S)—N-Hydroxy-3-(methoxymethyl)-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

35

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Into a 25-mL round-bottom flask, was placed methyl (S)-3-(methoxymethyl)-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (60.2 mg, 0.23 mmol, 1 equiv), THF/MeOH (4:1, 1.2 mL),  $NH_2OH$  (50% in water, 1499 mg, 22.72 mmol, 100 equiv), aq. 1N NaOH (0.45 mL, 2 equiv). The resulting solution was stirred for 1 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5  $\mu m$ , 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Detector: UV 254, 220 nm) to afford the title compound as a yellow solid (22 mg, 32% yield).  $^1H$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$ (ppm): 11.55-10.78 (m, 2H), 7.62-7.41 (m, 3H), 4.74-4.70 (d, J=16 Hz, 1H), 4.58-4.27 (m, 3H), 4.14-4.11 (m, 1H), 3.99-3.91 (m, 1H), 3.90-3.81 (m, 1H), 3.78-3.63 (m, 1H), 3.37-3.33 (d, J=16 Hz, 3H), 2.84 (s, 2H), 2.58 (s, 1H). MS: (ES, m/z): 267  $[M+H]^+$ .

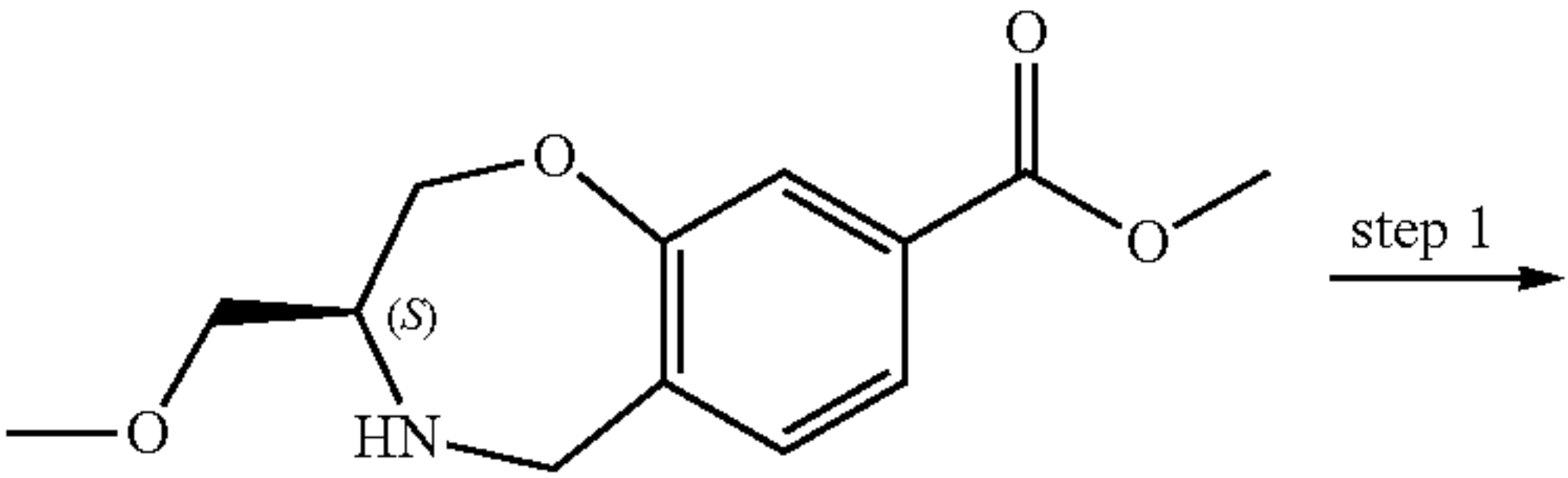


TABLE 27

The following compounds were prepared according to the method of Example 56, using (2S)-2-amino-3-methoxypropan-1-ol hydrochloride in Step 1 where appropriate.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 11.49-10.83 (m, 2H), 9.20 (br s, 1H), 7.6-7.34 (m, 3H), 4.73-3.43 (m, 10H), 2.96-2.84 (m, 3H) [M + H] <sup>+</sup>	
	(ES, m/z): 11.82-11.16 (m, 2H), 7.56-7.44 (m, 5H), 6.99-6.97 (d, J = 6 373 Hz, 2H), 4.81-4.77 (m 1H), 4.57-4.53 (m, 1H), 4.70-4.36 (m, [M + H] <sup>+</sup> 3H), 4.24 (m, 2H), 4.01 (m, 1H), 3.88-3.83 (m, 1H), 3.77 (s, 3H), 3.56 (s, 1H), 3.32-3.28 (m, 2H)	
	(ES, m/z): 11.45-11.08 (m, 1H), 10.71-10.53 (m, 1H), 9.58-8.69 (br s, 373 1H), 7.61-7.12 (m, 5H), 7.04-3.93 (m, 2H), 4.91-3.98 (m, [M + H] <sup>+</sup> 7H), 3.97-3.68 (m, 5H), 3.33-3.24 (s, 3H)	

Example 57

Preparation of (S)—N-hydroxy-3-(methoxymethyl)-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



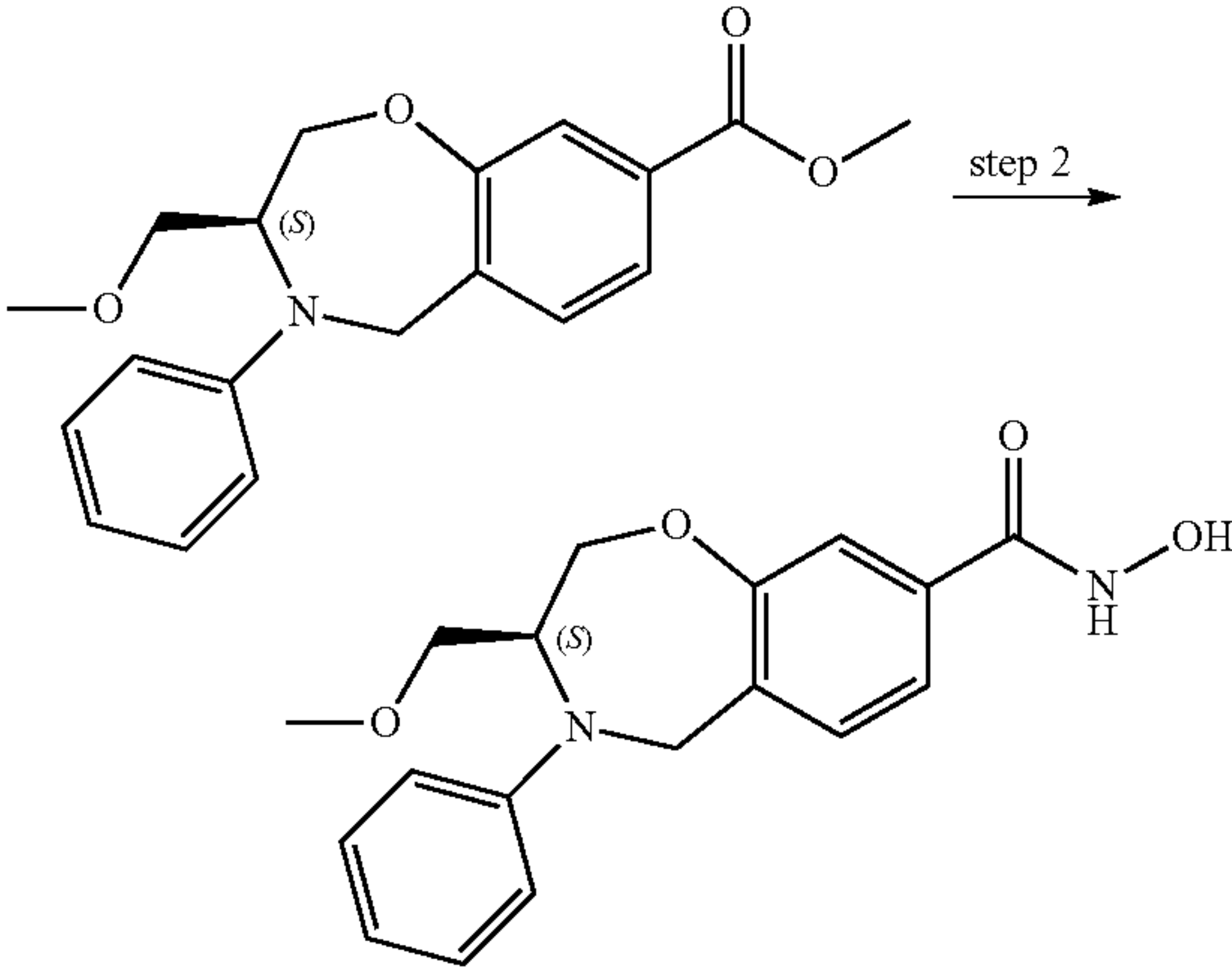
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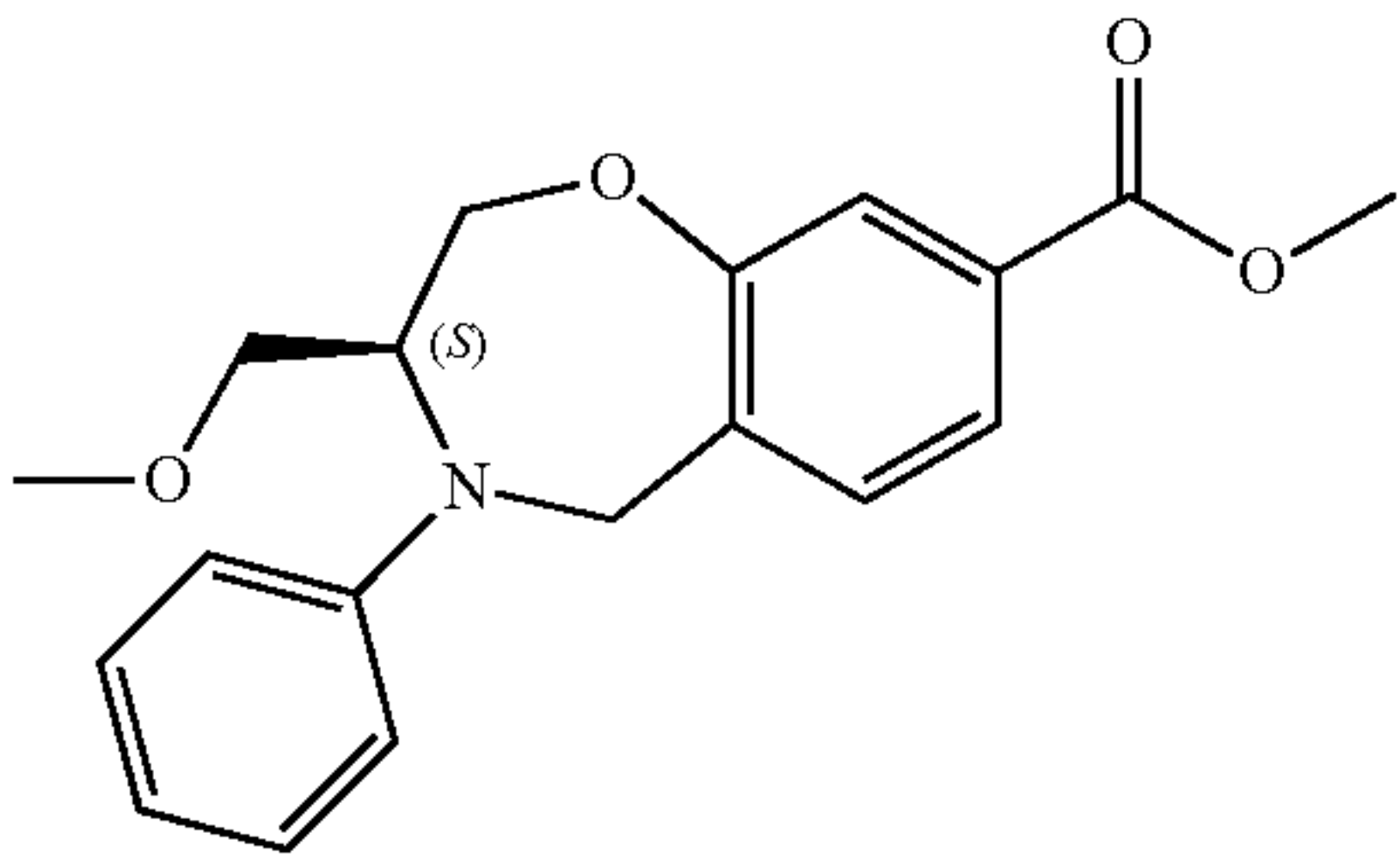
60

65



165

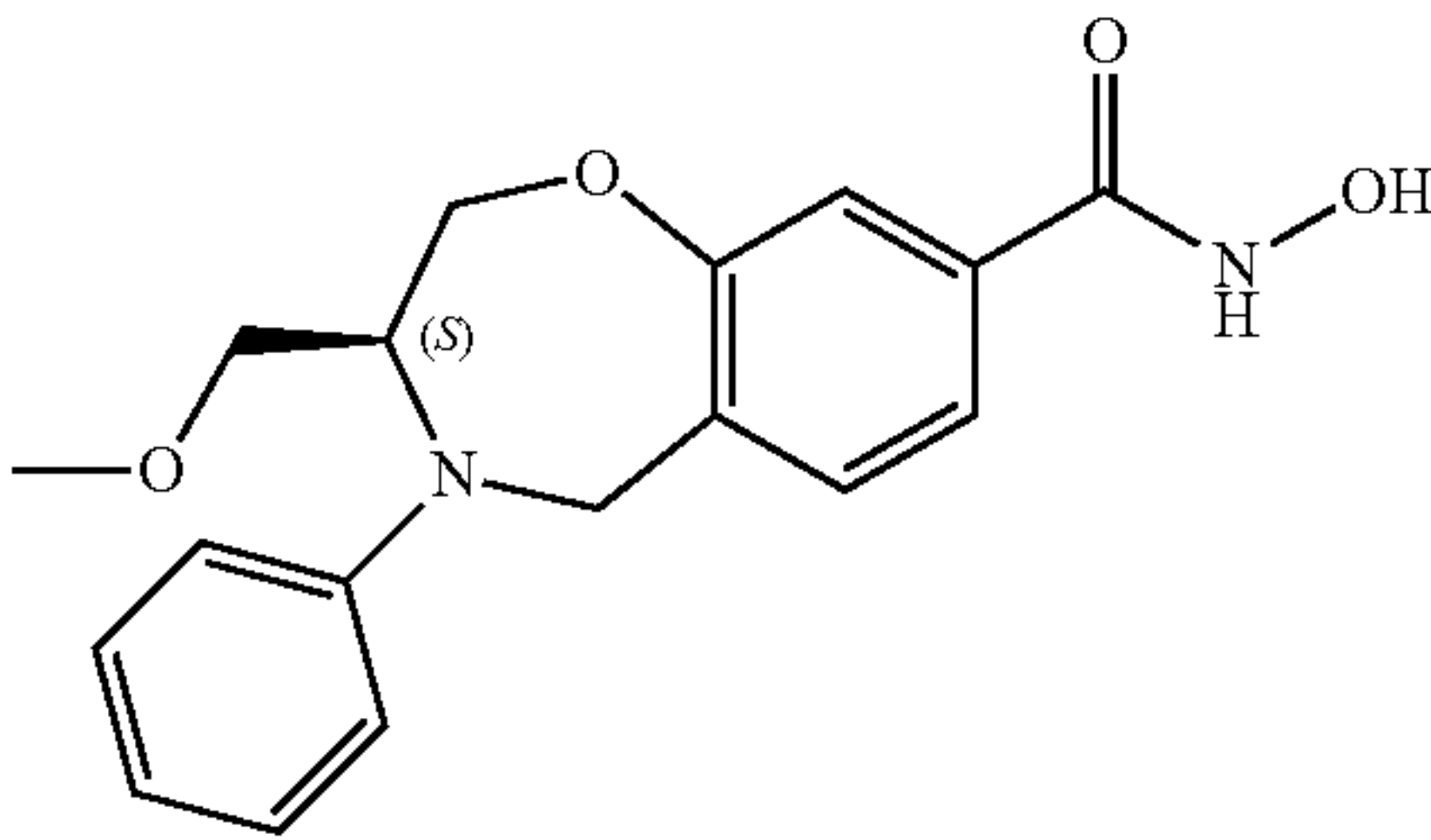
Step-1: Methyl (S)-3-(methoxymethyl)-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 50-mL round-bottom flask, was placed methyl (S)-3-(methoxymethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (200 mg, 0.80 mmol, 1 equiv), a solution of phenylboronic acid (291 mg, 2.39 mmol, 3 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), 4 Å molecular sieve (60 mg), Et<sub>3</sub>N (241 mg, 2.38 mmol, 3 equiv) and Cu(OAc)<sub>2</sub> (144 mg, 0.79 mmol, 1 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of H<sub>2</sub>O (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×50 mL). The combined organic layers were concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:10) to afford the title compound as a yellow solid (33 mg, 12% yield). MS: (ES, m/z): 328 [M+H]<sup>+</sup>.

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Step-2: (S)—N-Hydroxy-3-(methoxymethyl)-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



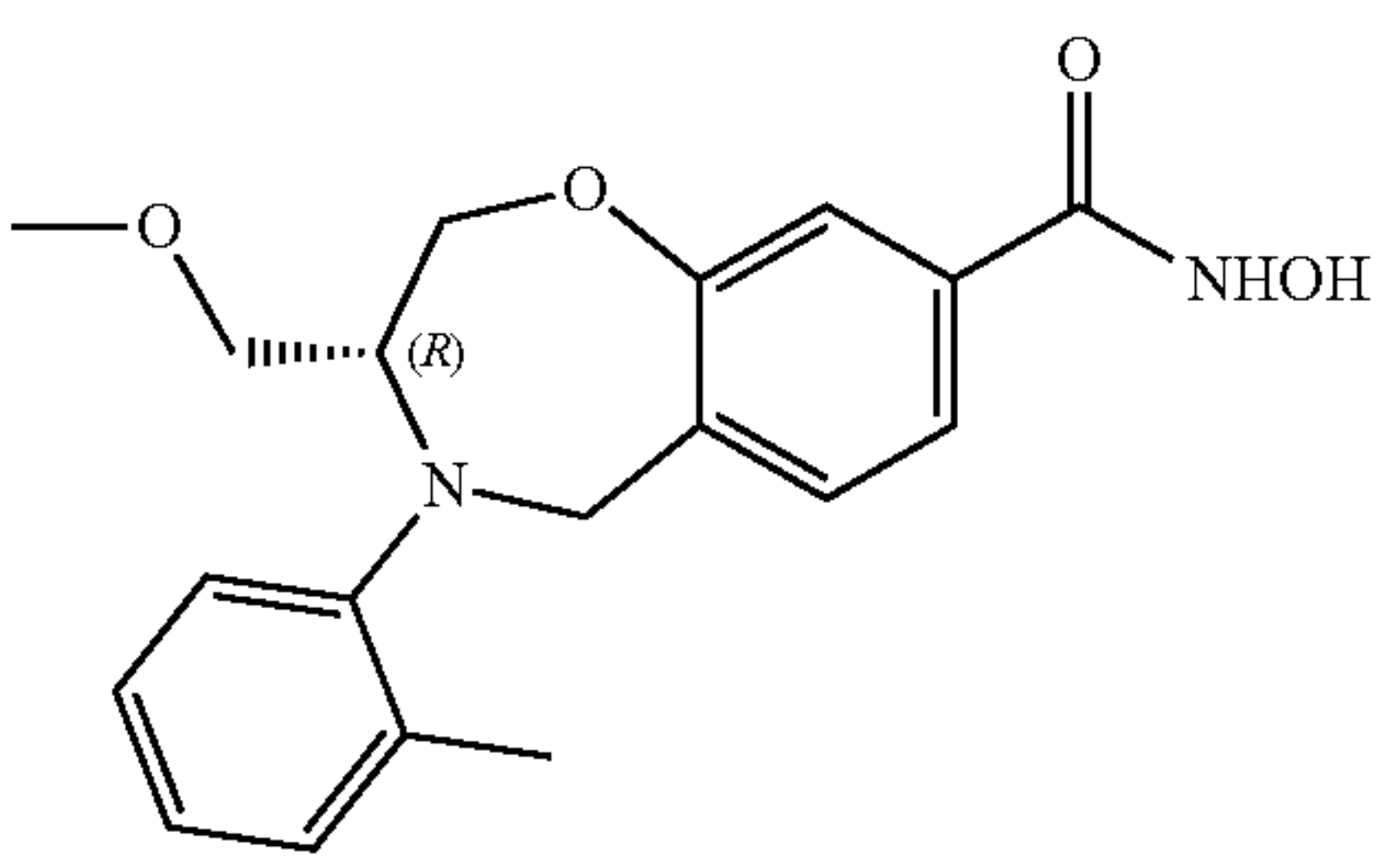
Into a 50-mL round-bottom flask, was placed a solution of methyl (S)-3-(methoxymethyl)-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (33 mg, 0.10 mmol, 1 equiv) in THF/MeOH (4:1, 2.5 mL), NH<sub>2</sub>OH (50% in water, 0.42 mL, 60 equiv), aq. 1N NaOH (0.2 mL, 2 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 30% B to 70% B in 10 min; Detector: UV 254, 220 nm). Aq. 1N HCl (0.1 mL) was added to the product fractions and lyophilized to afford the title compound as the HCl salt as a yellow solid (8.5 mg, 23% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.20 (br s, 1H), 7.48-7.46 (d, J=6 Hz, 1H), 7.35-7.32 (d, J=9 Hz, 1H), 7.10-7.03 (m, 3H), 6.70-6.67 (d, J=9 Hz, 2H), 6.58-6.54 (m, 1H), 5.09-5.03 (d, J=18 Hz, 1H), 4.51-4.27 (m, 4H), 3.59-3.57 (d, J=6 Hz, 2H), 3.33 (s, 3H). MS: (ES, m/z): 329 [M+H]<sup>+</sup>.

TABLE 28

The following compounds were prepared according to the method of Example 57, using (2S)-2-amino-3-methoxypropan-1-ol hydrochloride in Step 1 where appropriate.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 329 [M + H] <sup>+</sup>	11.18-11.05 (br s, 1H), 7.49-7.47 (d, J = 8 Hz, 1H), 7.35-7.33 (d, J = 8 Hz, 1H), 7.11-7.04 (m, 3H), 6.70-6.68 (d, J = 8 Hz, 2H), 6.59-6.52 (m, 1H), 5.09-5.05 (d, J = 16 Hz, 1H), 4.55-4.46 (m, 1H), 4.41-4.22 (m, 3H), 3.59-3.58 (d, J = 4 Hz, 2H), 3.33 (s, 3H)
	(ES, m/z): 343 [M + H] <sup>+</sup>	11.13 (br s, 1H), 9.60 (br s, 1H), 7.27-7.20 (m, 3H), 7.17-7.07 (m, 3H), 6.97-6.93 (m, 1H), 4.46-4.41 (m, 3H), 4.26-4.22 (d, J = 16 Hz, 1H), 3.80-3.77 (m, 1H), 3.51-3.41 (m, 1H), 3.31-3.27 (m, 1H), 3.22 (s, 3H), 2.17 (s, 3H).

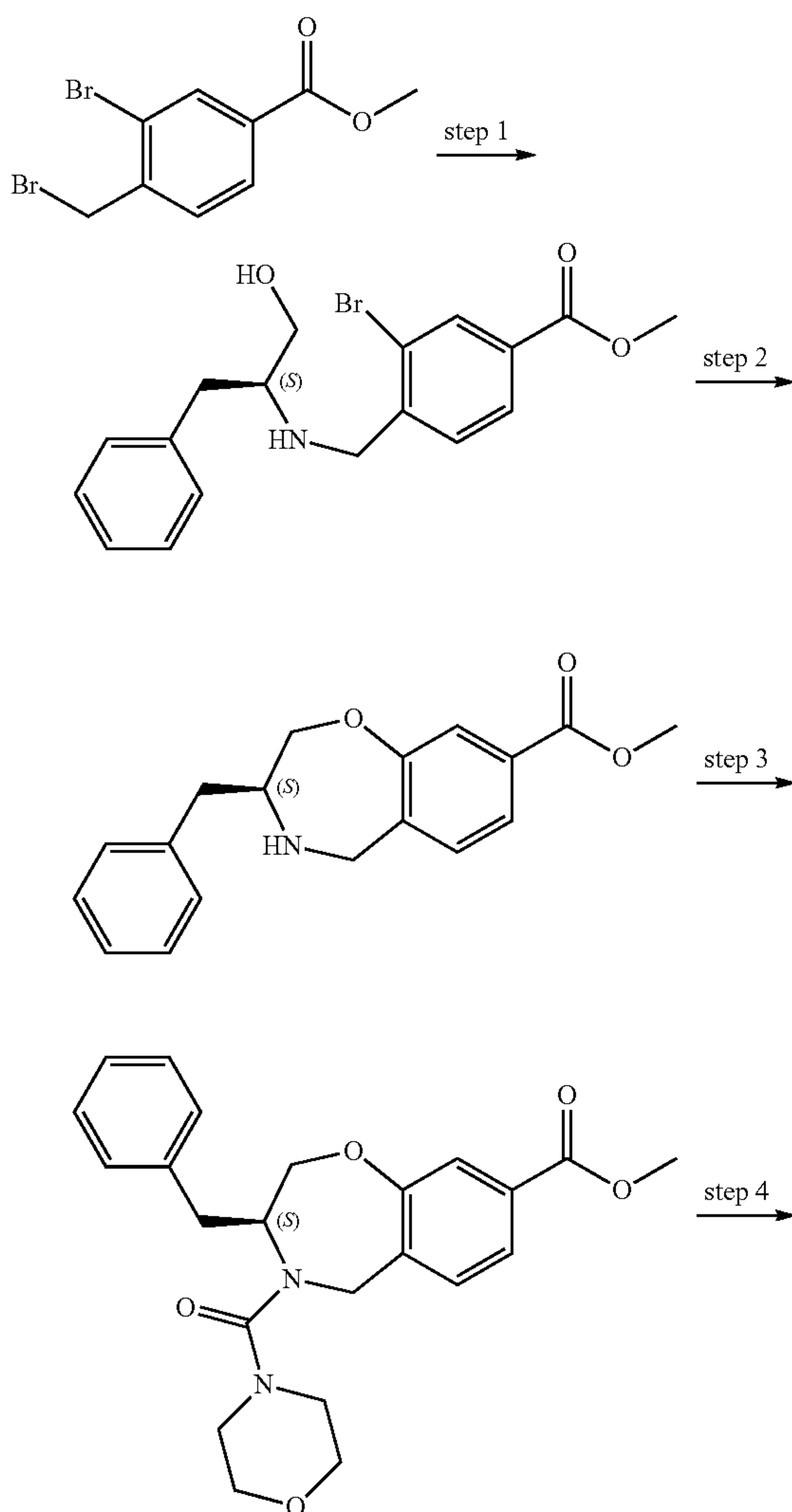


TABLE 28-continued

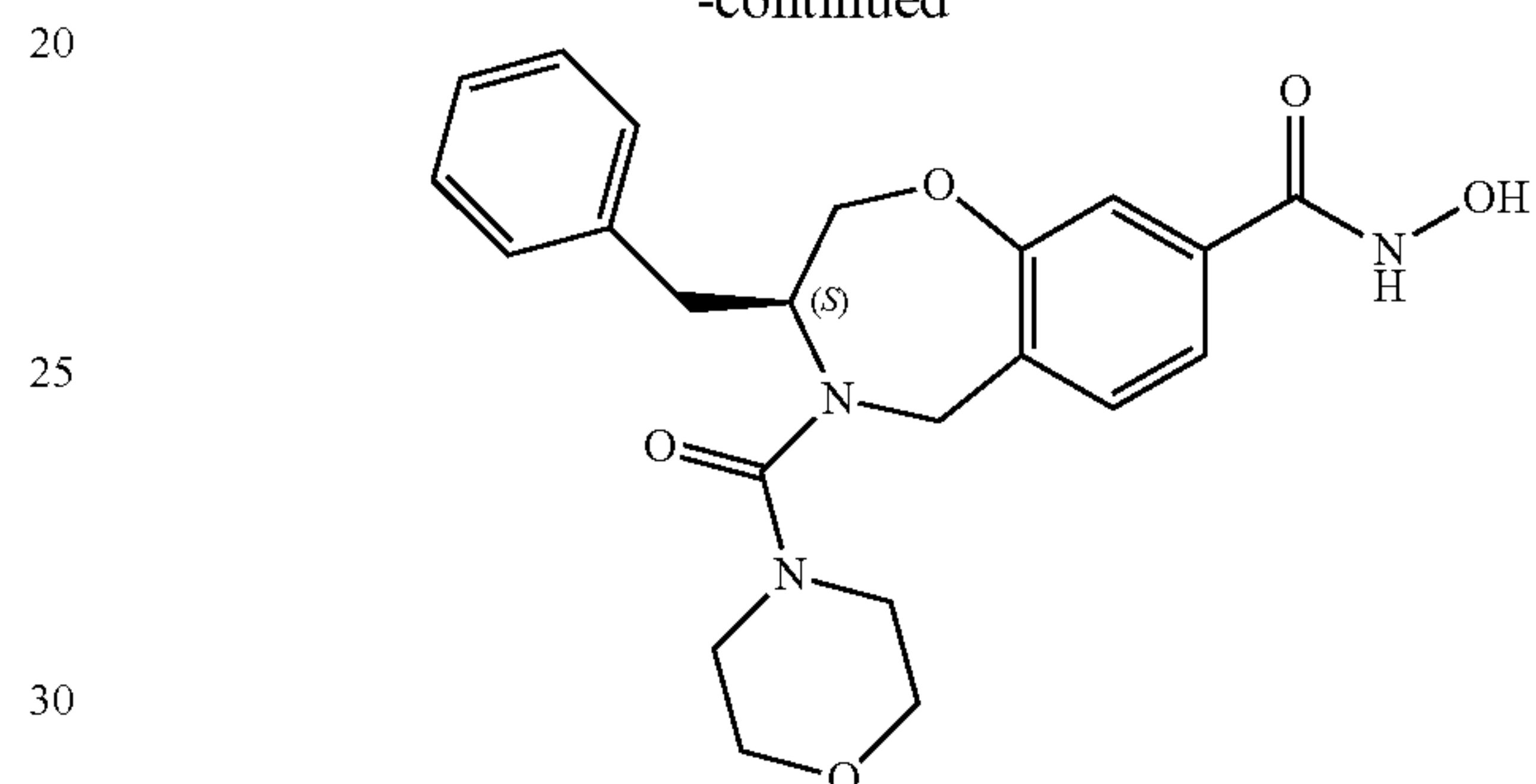
The following compounds were prepared according to the method of Example 57, using (2S)-2-amino-3-methoxypropan-1-ol hydrochloride in Step 1 where appropriate.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 343 [M + H] <sup>+</sup>	11.23 (br s, 1H), 7.20-7.27 (m, 3H), 7.07-7.17 (m, 3H), 6.93-6.97 (t, J = 7.2 Hz, 1H), 4.41-4.46 (m, 3H), 4.22-4.26 (d, J = 16.4 Hz, 1H), 3.77-3.80 (m, 1H), 3.47-3.51 (t, J = 8.8 Hz, 1H), 3.27-3.31 (m, 1H), 3.22 (s, 3H), 2.17 (s, 3H)

## Example 58

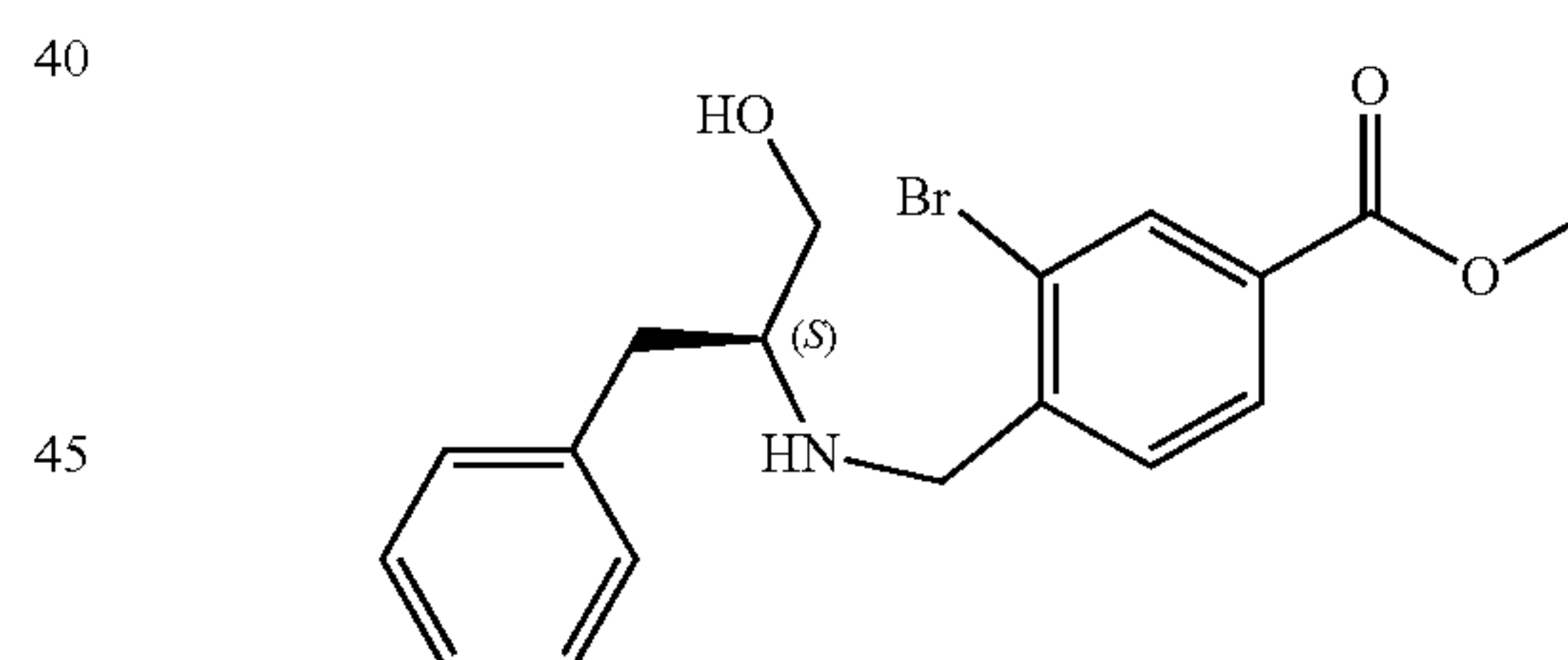
Preparation of (S)-3-benzyl-N-hydroxy-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



-continued



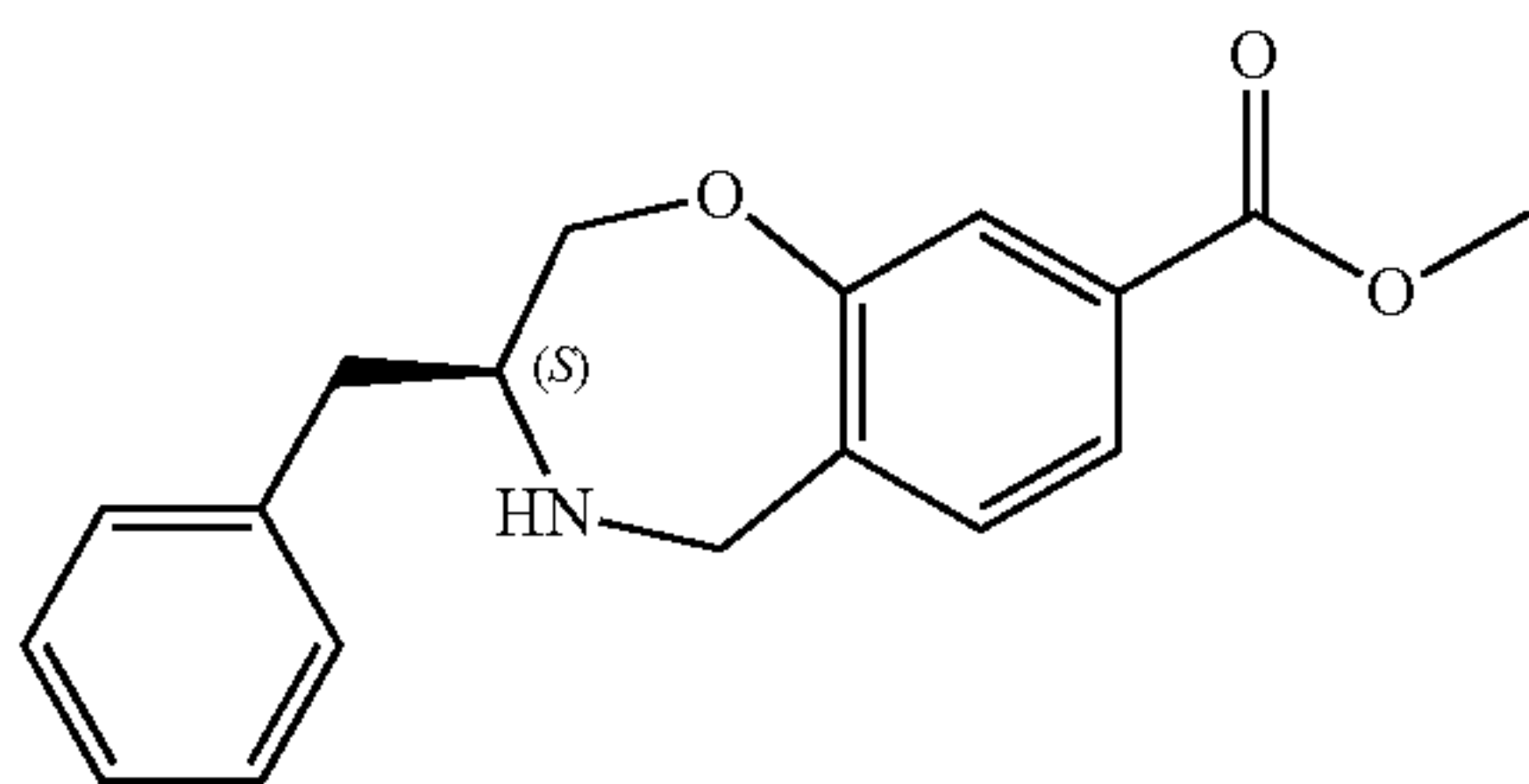
Step-1: Methyl (S)-3-bromo-4-(((1-hydroxy-3-phenylpropan-2-yl)amino)methyl)benzoate



Into a 40-mL scintillation vial was placed (S)-2-amino-3-phenylpropan-1-ol (271 mg, 1.79 mmol, 1.30 equiv), K<sub>2</sub>CO<sub>3</sub> (572 mg, 4.14 mmol, 3.00 equiv) and MeCN (15 mL). The resulting slurry was cooled to 0° C. in an ice-water bath. Next, a solution of methyl 3-bromo-4-(bromomethyl)benzoate (425 mg, 1.380 mmol, 1.00 equiv) in MeCN (3 mL) was added dropwise over 10 min while maintaining the internal temperature at 0° C. The ice bath was removed and the resulting slurry was allowed to slowly warm to room temperature. Stirring continued at room temperature for 16 h. The reaction was concentrated under reduced pressure to remove most of the MeCN. The concentrated mixture was partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL). The organic phase was washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford the title compound as a yellow oil (628 mg), which was used without further purification. MS: (ES, m/z): 379 [M+H]<sup>+</sup>.

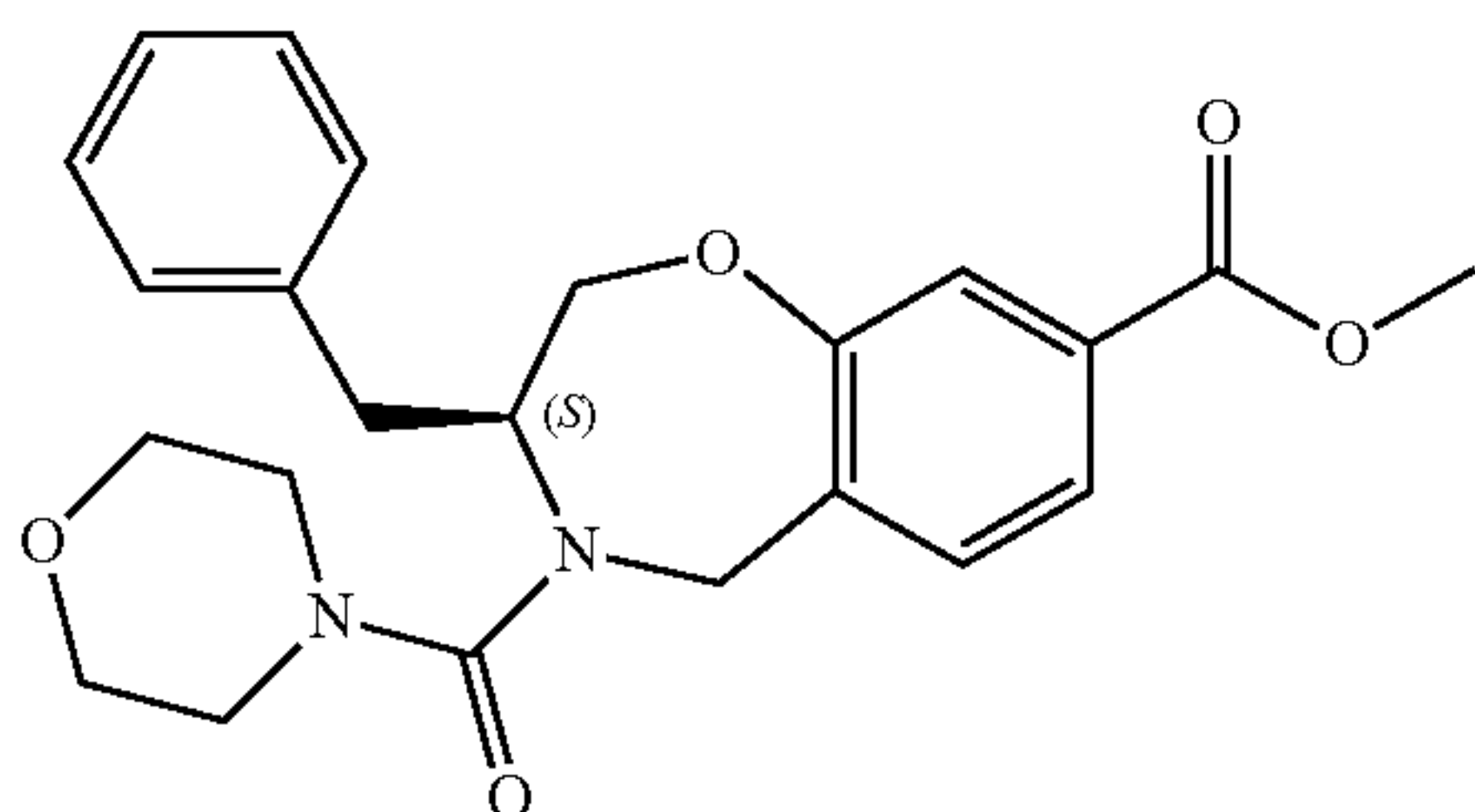
## 169

Step-2: Methyl (S)-3-benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 40-mL scintillation vial was placed methyl (S)-3-bromo-4-(((1-hydroxy-3-phenylpropan-2-yl)amino)methyl)benzoate hydrochloride (522 mg, 1.39 mmol, 1 equiv) in isopropanol (5 mL).  $K_2CO_3$  (381 mg, 2.76 mmol, 2 equiv) was added followed by CuI (52.6 mg, 0.276 mmol, 0.2 equiv). The resulting solution was heated to reflux for 18 h. The resulting mixture was filtered through a celite pad and washed with isopropanol (10 mL). The filtrate was reduced in volume to ~5 mL and 10N HCl (1.1 equiv) was added dropwise, with stirring, to the filtrate. The resulting slurry was cooled in an ice bath for 30 min before being filtered to afford the title compound as the HCl salt as a yellow solid (252 mg, 49.3% yield).  $^1H$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$ (ppm): 7.68-7.77 (m, 1H), 7.58-7.66 (m, 1H), 7.54 (d,  $J$ =1.8 Hz, 1H), 7.23-7.45 (m, 4H), 4.36-4.58 (m, 2H), 4.26 (br d,  $J$ =11.4 Hz, 1H), 3.74-4.05 (m, 4H), 3.42 (s, 1H), 3.07-3.27 (m, 2H), 2.90 (br dd,  $J$ =13.6, 9.2 Hz, 1H), 1.03 (d,  $J$ =6.2 Hz, 1H). MS: (ES,  $m/z$ ): 298  $[M+H]^+$ .

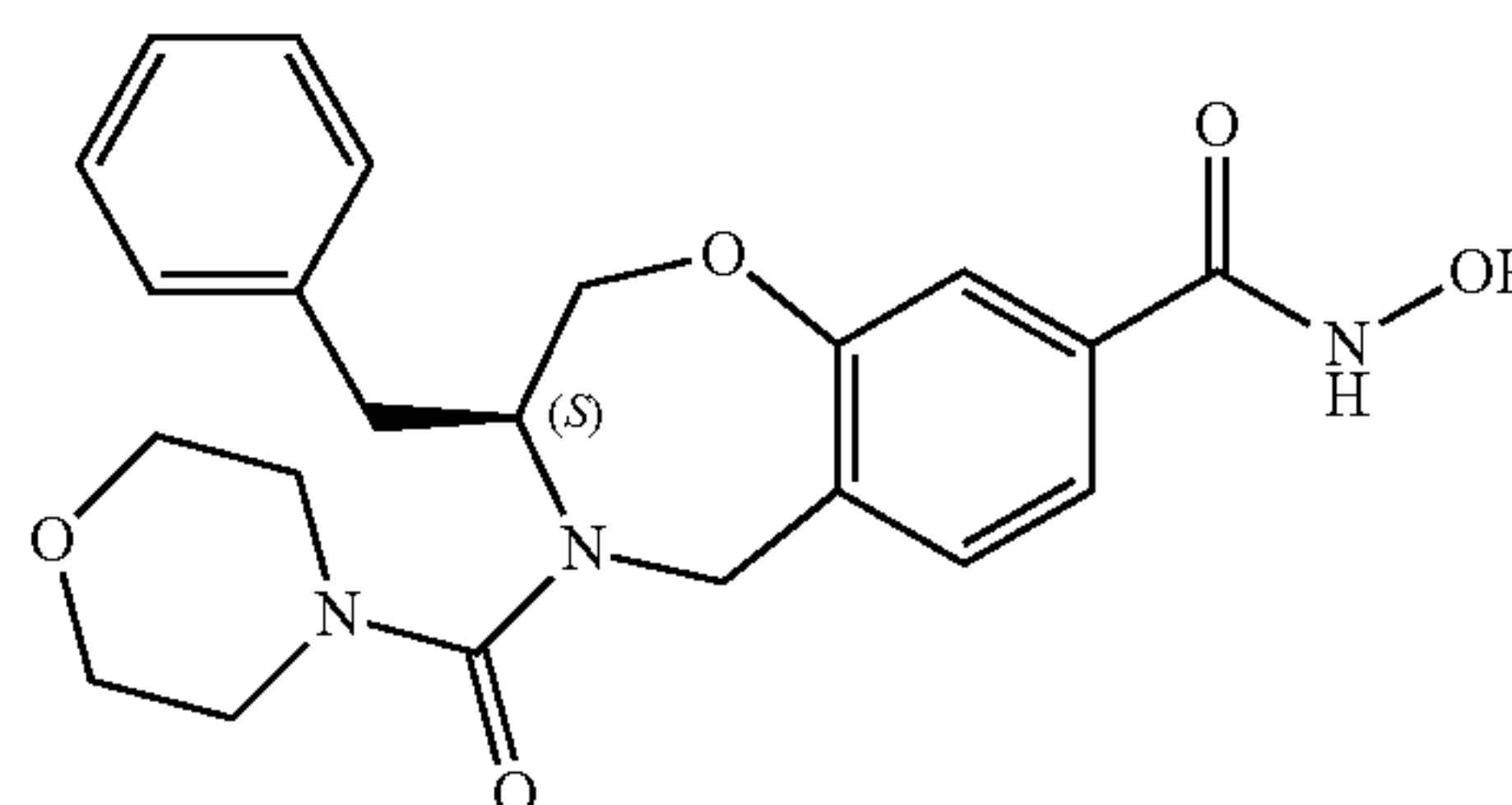
Step-3: Methyl (S)-3-benzyl-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



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Into a 4-mL vial equipped with a stir bar was placed a solution of triphosgene (17.8 mg, 0.060 mmol, 0.4 equiv) in  $CH_2Cl_2$  (2 mL). Next, a solution of methyl (S)-3-benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate hydrochloride (50 mg, 0.150 mmol, 1 equiv),  $Et_3N$  (0.063 mL, 0.449 mmol, 3 equiv), and morpholine (13.5 mg, 0.150 mmol, 1 equiv) and  $CH_2Cl_2$  (2 mL) was added. The resulting solution was stirred at room temperature for 16 h. The reaction was concentrated to dryness to afford the title compound (61.4 mg) which was used without further purification. MS: (ES,  $m/z$ ): 410  $[M+H]^+$ .

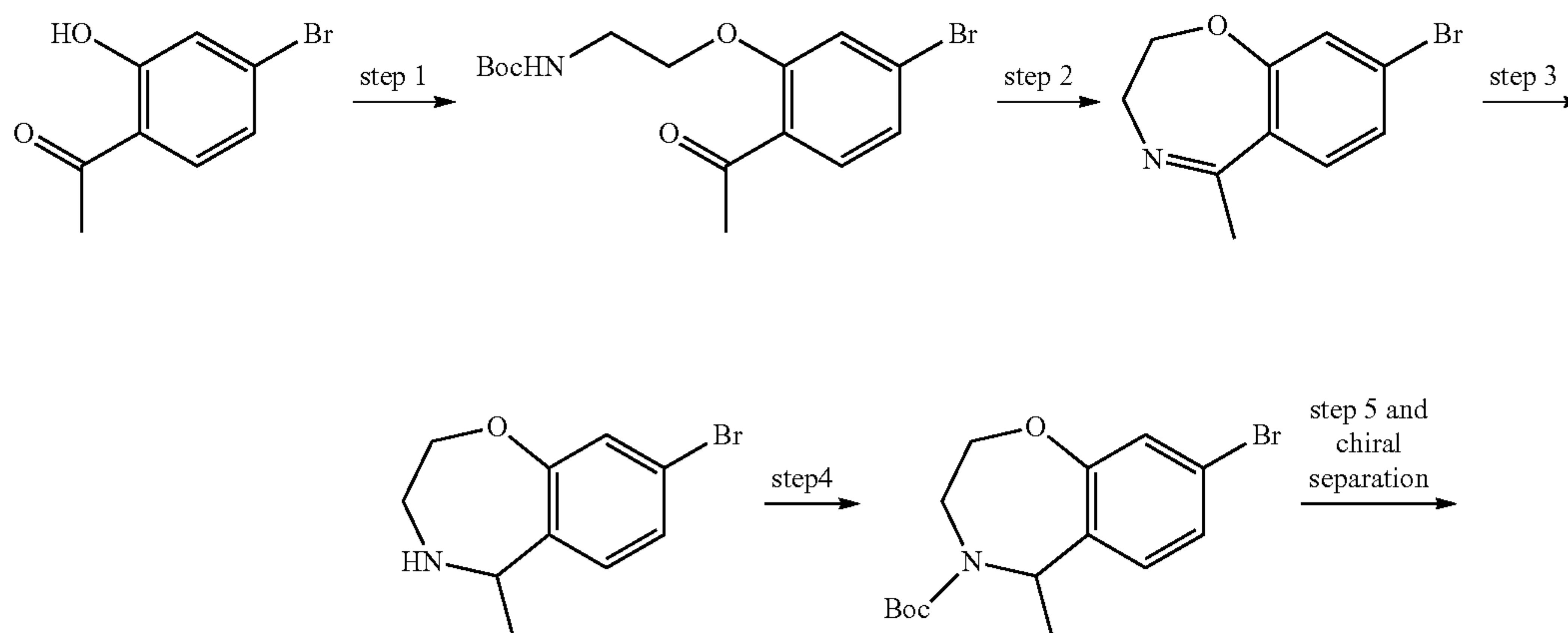
Step-3: (S)-3-Benzyl-N-hydroxy-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 4-mL vial was placed methyl (S)-3-benzyl-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (61.6 mg, 0.150 mmol, 1 equiv),  $NH_2OH$  (50% in water, 0.1 mL, 1.5 mmol, 10 equiv), and aq. 1N NaOH (0.3 mL, 0.3 mmol, 2 equiv) in a solution of THF/MeOH (4:1, 2.0 mL). The resulting solution was stirred at room temperature for 2 h, then concentrated. The residue was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5  $\mu m$ , 19x50 mm; Mobile Phase A: Water/0.1% formic acid; Mobile Phase B: MeCN/0.1% formic acid; Flow rate: 23 mL/min; Gradient: 15% B to 65% B in 8 min; Detector: UV 254, 220 nm) to afford the title compound as a white solid (4.5 mg, 11% yield). MS: (ES,  $m/z$ ): 412  $[M+H]^+$ .

## Example 59

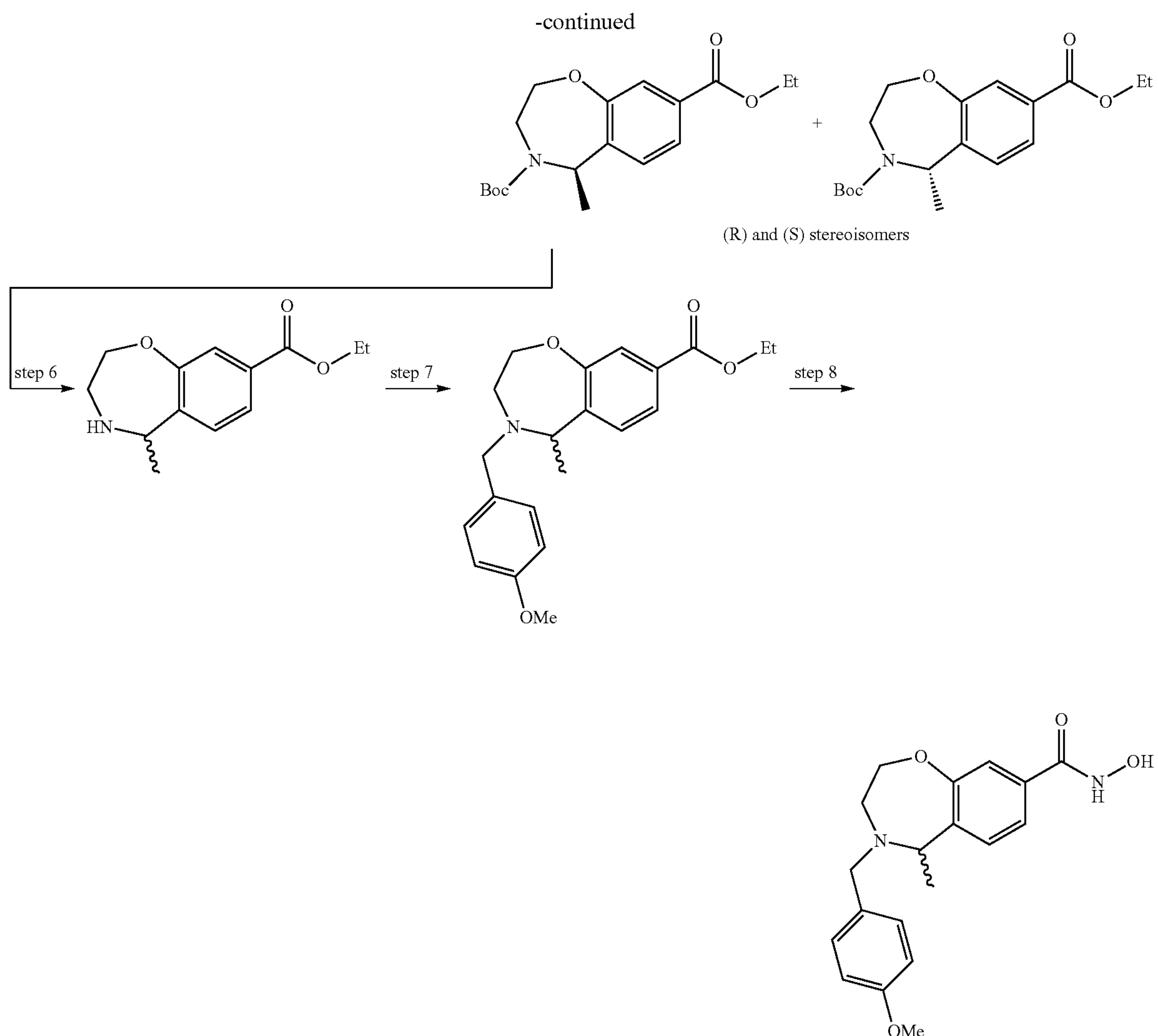
Preparation of (R)-N-hydroxy-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



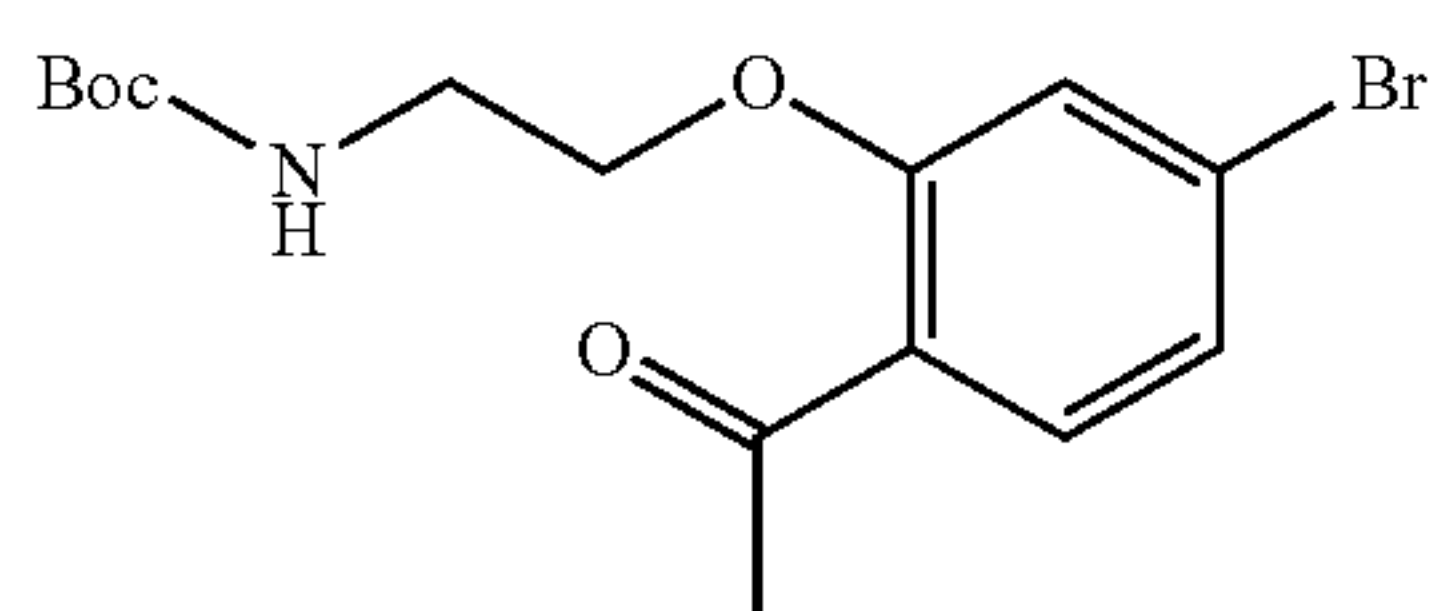


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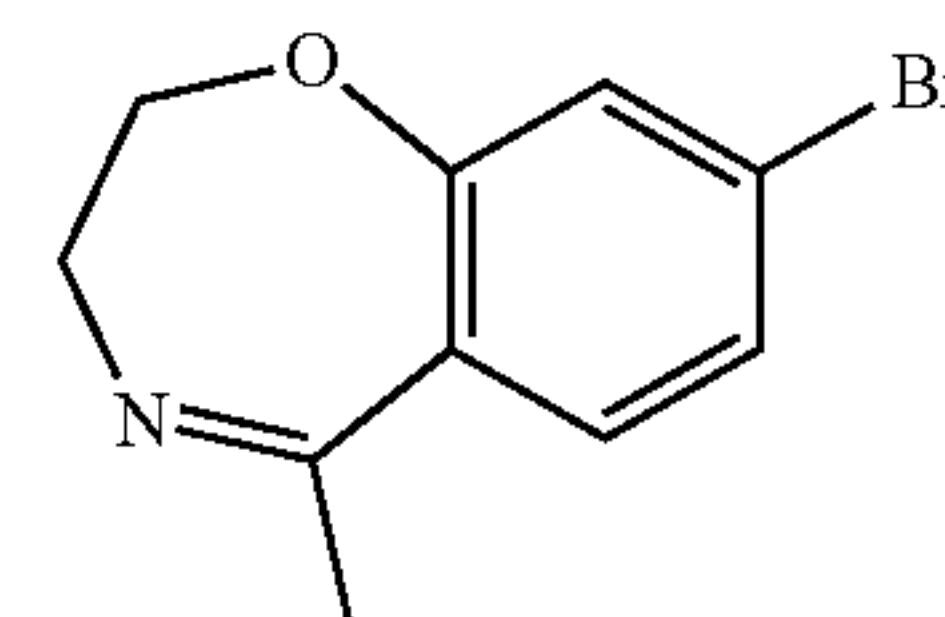
Step-1: tert-Butyl  
(2-(2-acetyl-5-bromophenoxy)ethyl)carbamate



Into a 500-mL 3-necked round-bottom flask, was placed 1-(4-bromo-2-hydroxyphenyl)ethan-1-one (30 g, 139 mmol, 1 equiv) in DMF (150 mL),  $K_2CO_3$  (29 g, 209 mmol, 1.5 equiv), potassium iodide (23.2 g, 1 equiv) and tert-butyl N-(2-bromoethyl)carbamate (47 g, 209 mmol, 1.5 equiv). The resulting mixture was stirred overnight at 50° C. The solids were filtered out. The filtrate was quenched with of  $H_2O$  (50 mL) and extracted with EtOAc (5×100 mL). The combined organic layers were washed with brine (3×50 mL), dried over anhydrous  $Na_2SO_4$ , filtered, and concentrated under vacuum. The residue was triturated with a

solution of EtOAc/pet. ether (1:10, 100 mL) to afford the title compound as an off-white solid (42 g, 84% yield). MS: (ES, m/z): 358  $[M+H]^+$ .

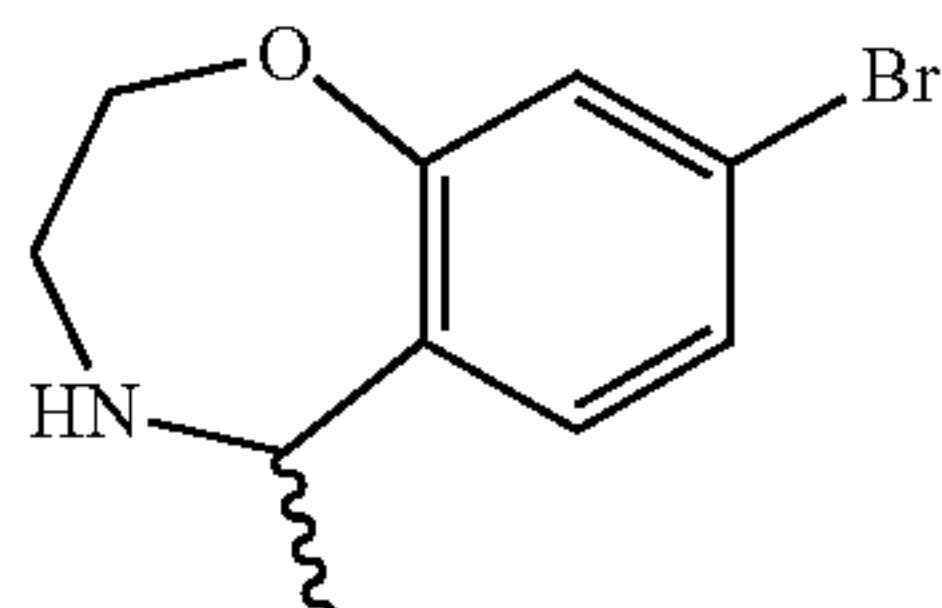
Step-2: 8-Bromo-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine



Into a 500-mL round-bottom flask, was placed tert-butyl 2-(2-acetyl-5-bromophenoxy)ethylcarbamate (23 g, 64.20 mmol, 1 equiv) in  $CH_2Cl_2$  (100 mL) and TFA (25 mL). The resulting solution was stirred overnight at room temperature, then concentrated under vacuum to afford the title compound as a yellow solid (15.4 g), which was used without further purification. MS: (ES, m/z): 240  $[M+H]^+$ .

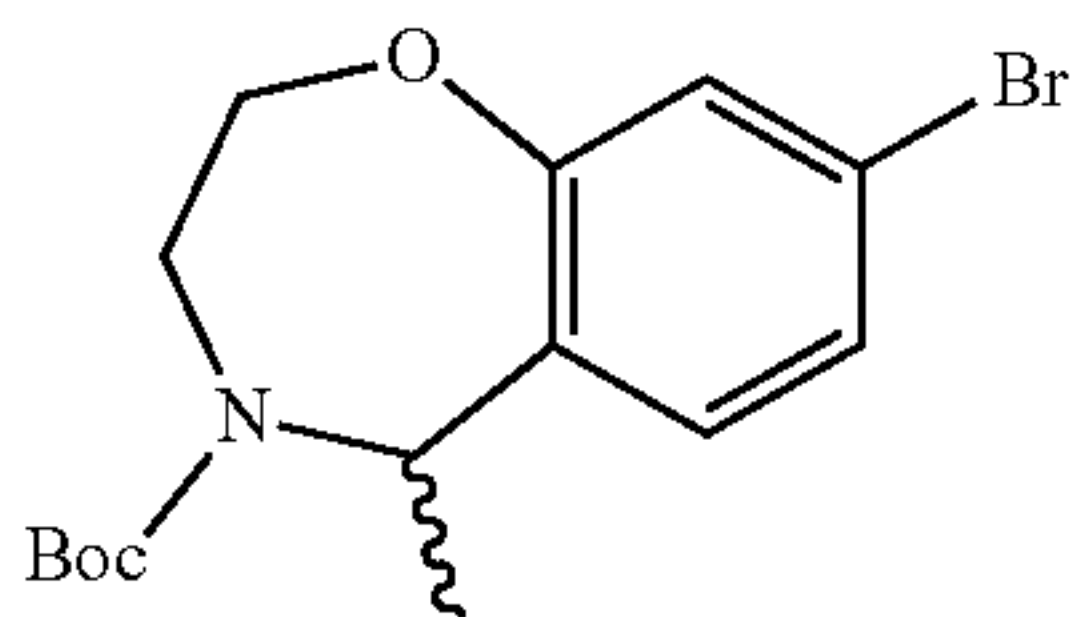
## 173

Step-3: 8-Bromo-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine



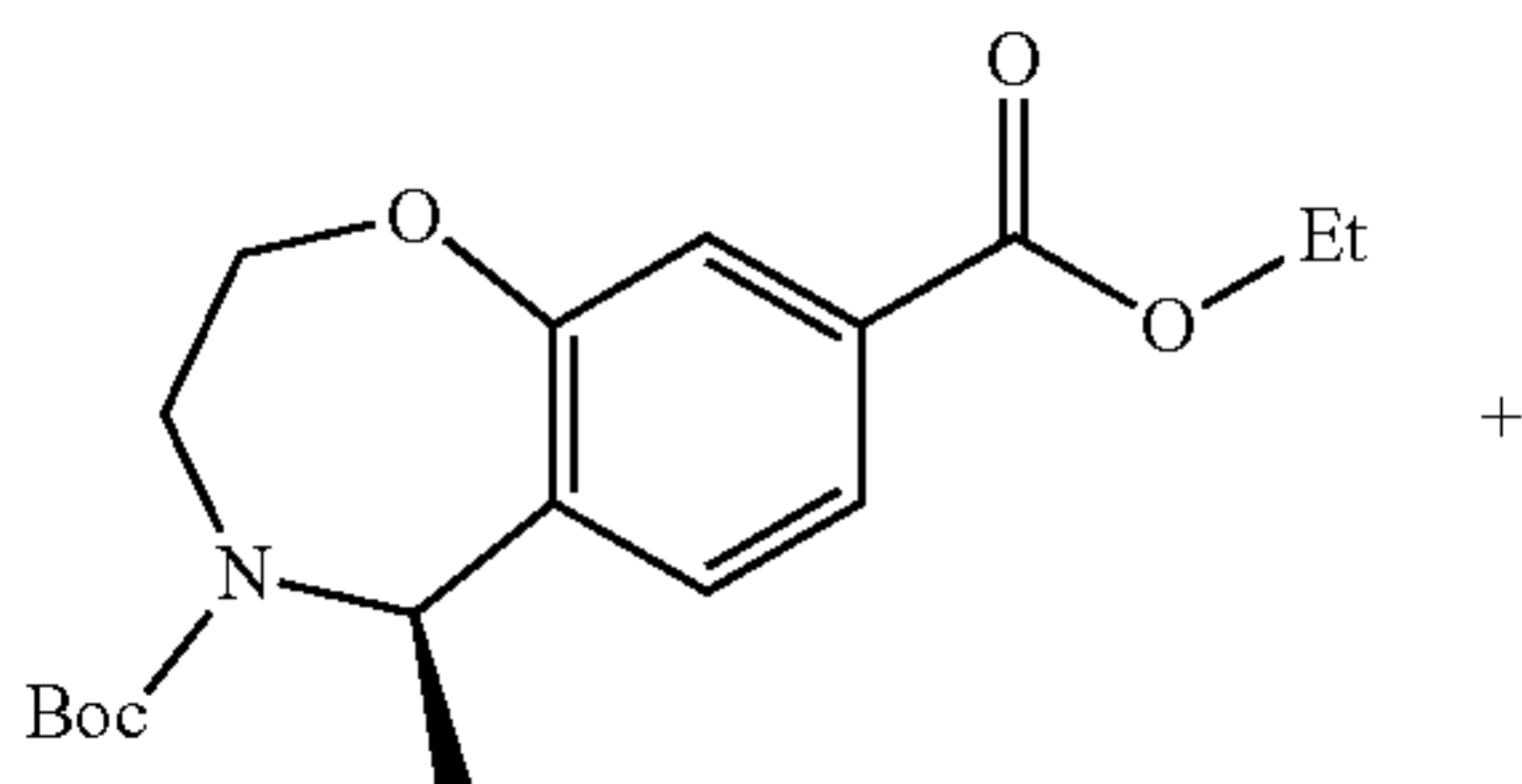
Into a 500-mL round-bottom flask, was placed a solution of 8-bromo-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine (15.4 g, 64.14 mmol, 1 equiv) in MeOH (200 mL). The pH value of the solution was adjusted to 7 with anhydrous NaOAc at 0° C. Then Na(CN)BH<sub>3</sub> (18.1 g, 288 mmol, 4.5 equiv) was added at 0° C. The resulting mixture was stirred for 4 h at room temperature and concentrated under vacuum. H<sub>2</sub>O (50 mL) was added to the residue and the solids were collected by filtration to afford the title compound as a white solid (15 g). MS: (ES, m/z): 242 [M+H]<sup>+</sup>.

Step-4: tert-Butyl 8-bromo-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate



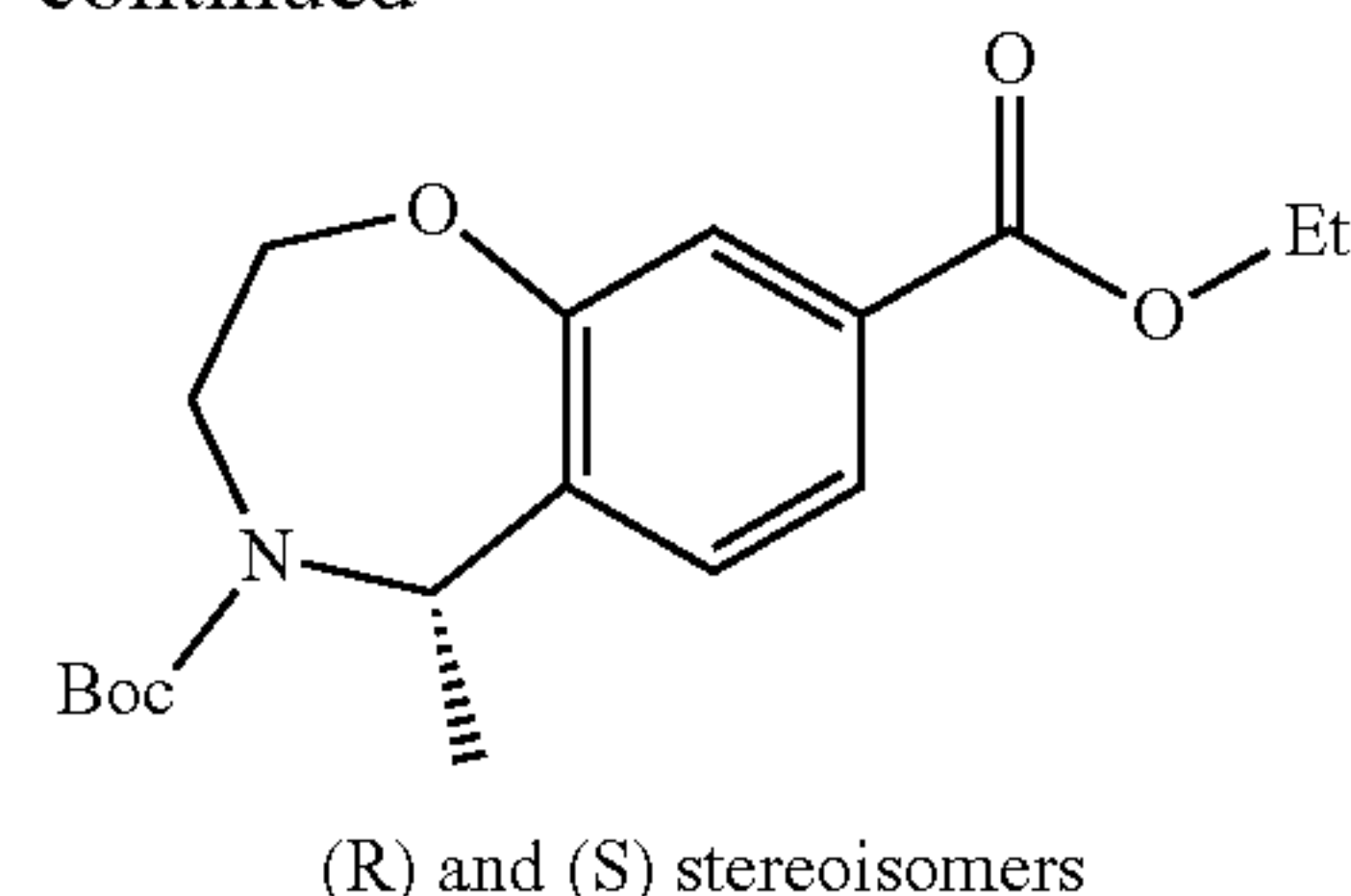
Into a 500-mL round-bottom flask, was placed tert-butyl 8-bromo-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate (9 g, 37.17 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (80 mL), Et<sub>3</sub>N (11.25 g, 111 mmol, 3 equiv) and di-tert-butyl dicarbonate (12.1 g, 55.44 mmol, 1.5 equiv). The resulting solution was stirred overnight at room temperature, then concentrated under vacuum. The crude product was purified by Flash-Prep-HPLC (Column: silica gel; Mobile Phase A: pet. ether, Mobile Phase B: EtOAc; Gradient: 0% B to 10% B in 50 min; Detector: 254 nm) to afford the title compound as white solid (11 g, 86% yield). MS: (ES, m/z): 342 [M+H]<sup>+</sup>.

Step-5: 4-(tert-Butyl) 8-ethyl (R)-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxylate and 4-(tert-butyl) 8-ethyl (S)-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxylate



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-continued



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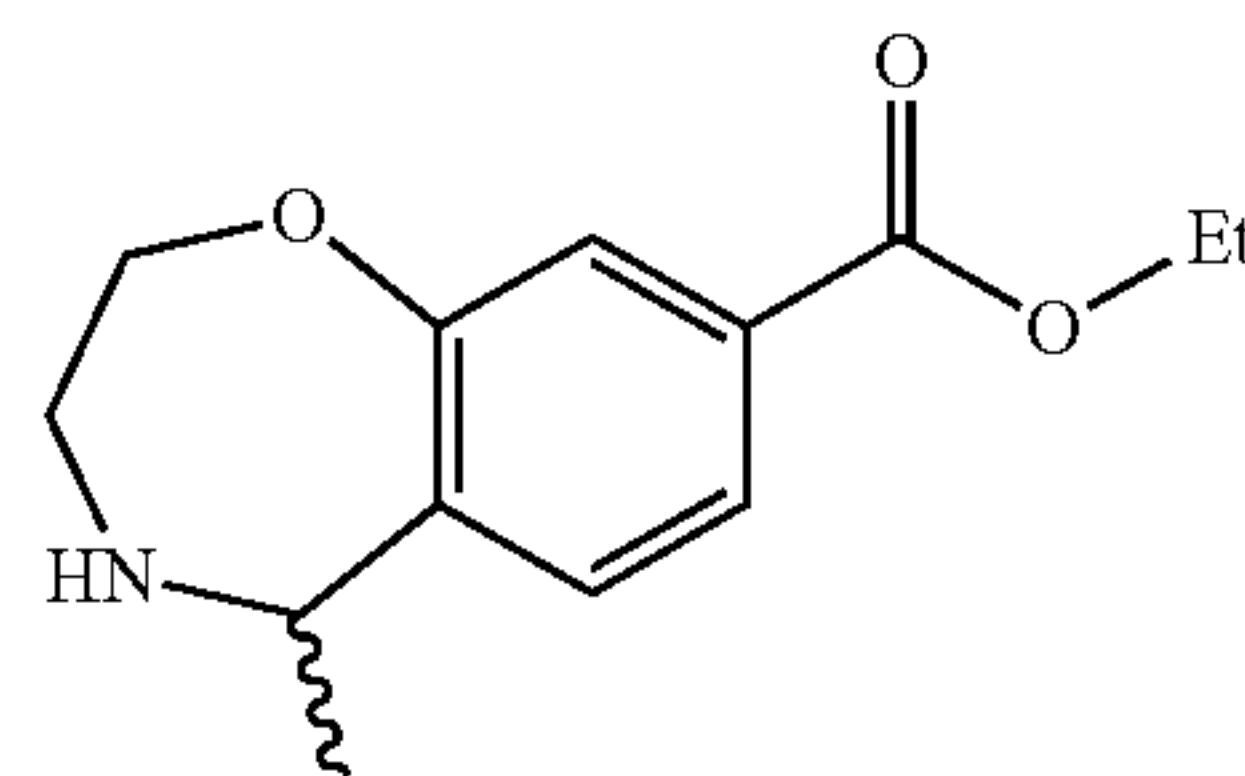
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Into a 50-mL sealed tube, was placed tert-butyl 8-bromo-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate ((2.5 g, 7.33 mmol, 1 equiv) in EtOH (25 mL), Et<sub>3</sub>N (2.22 g, 22 mmol, 3 equiv) and Pd(dppf)Cl<sub>2</sub> (0.534 g, 0.73 mmol, 0.1 equiv). To the above reaction mixture CO (g) (60 atm) was introduced. The resulting mixture was stirred overnight at 120° C., then concentrated under vacuum. The crude product was purified by Flash-Prep-HPLC (Column: silica gel; Mobile Phase A: pet. ether, Mobile Phase B: EtOAc; Gradient: 0% B to 10% B in 30 min; Detector: 254 nm) to afford the title compounds as a racemic mixture. The racemate was then purified by Prep-SFC (Column: (R,R) WHELK-01 Kromasil, 10 μm, 21.1×250 mm; Mobile Phase A: 75% CO<sub>2</sub>, 25% isopropanol (0.2% N,N-diethylaniline); Flow rate: 45 mL/min; Detector: UV 254 nm) to afford the single isomers as a light yellow oil (first eluting isomer: 540 mg, 21.9% yield; second eluting isomer: 680 mg, 27.7% yield). MS: (ES, m/z): 336 [M+H]<sup>+</sup>.

Step-6: Ethyl (R)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

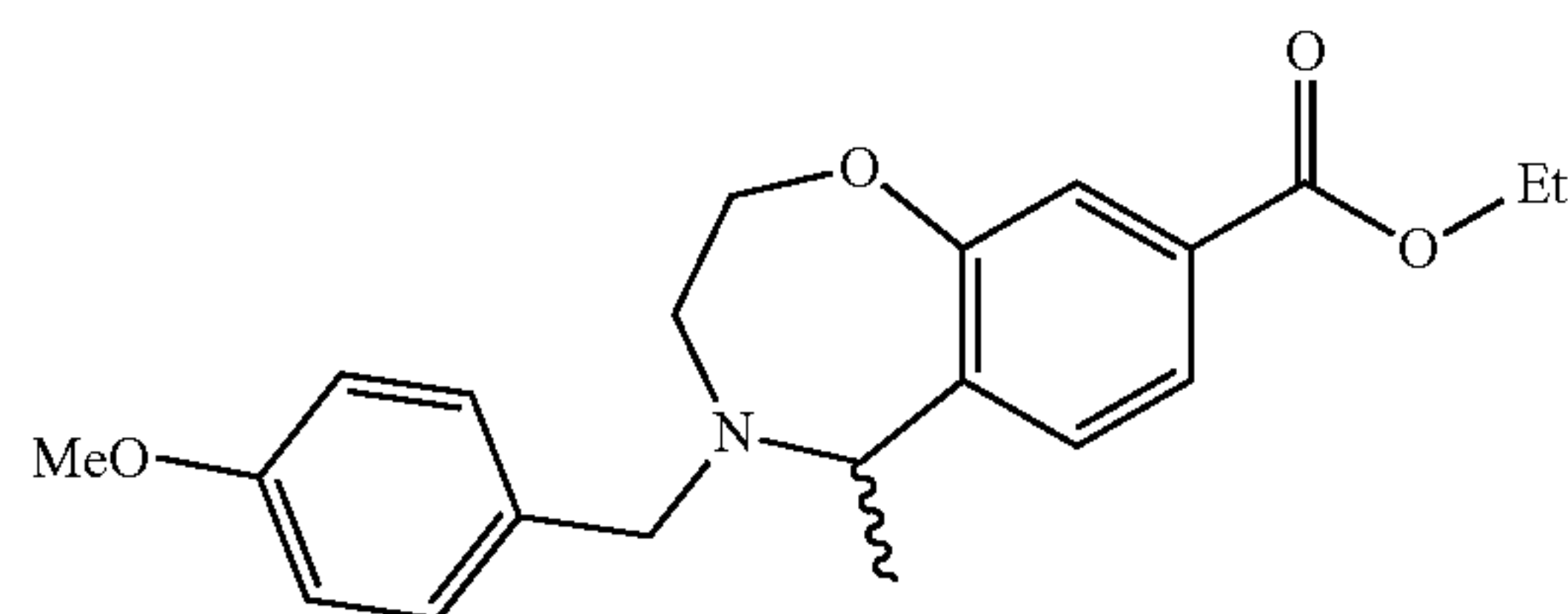


Into a 25-mL round-bottom flask, was placed the first eluting isomer from Step 5 (4-(tert-butyl) 8-ethyl (R)-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxylate) (540 mg, 1.61 mmol, 1 equiv), CH<sub>2</sub>Cl<sub>2</sub> (5 mL), and TFA (2 mL). The resulting solution was stirred overnight at room temperature, then concentrated under vacuum. The crude product was purified by Flash-Prep-HPLC (Column: C18 silica gel; Mobile Phase A: H<sub>2</sub>O/0.05% TFA, Mobile Phase B: MeCN; Gradient: 5% B to 50% B in 30 min; Detector: 254 nm) to afford the title compound as a white solid (450 mg), which was used without further purification. MS: (ES, m/z): 236 [M+H]<sup>+</sup>.



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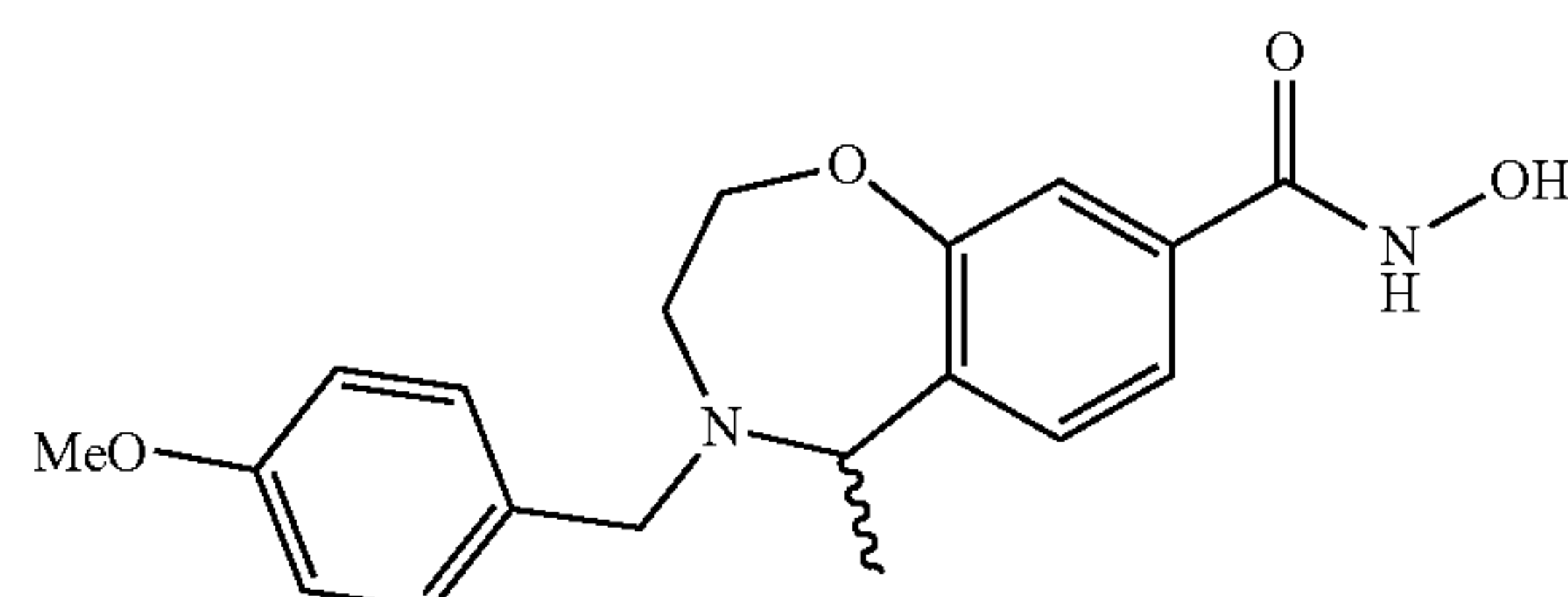
Step-7: Ethyl (R)-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Into a 25-mL round-bottom flask, was placed ethyl (R)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (100 mg, 0.43 mmol, 1 equiv) and 4-methoxybenzaldehyde (57 mg, 0.42 mmol, 1 equiv) in MeOH (2 mL). After stirring for 30 min, Na(CN)BH<sub>3</sub> (80 mg, 1.27 mmol, 3 equiv) was added at 0° C. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of H<sub>2</sub>O (2 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5×10 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a yellow oil (50 mg, 34% yield). MS: (ES, m/z): 356 [M+H]<sup>+</sup>.

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Step-8: (R)—N-Hydroxy-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Into a 25-mL round-bottom flask, was placed ethyl (R)-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (50 mg, 0.14 mmol, 1 equiv), THF/MeOH (4/1, 2 mL), NH<sub>2</sub>OH (50% in water, 579 mg, 60 equiv), aq. 1N NaOH (0.28 mL, 2 equiv). The resulting solution was stirred for 8 h at room temperature. The mixture was purified by Prep-HPLC (Column: Sunfire C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN; Flow rate: 0.7 mL/min; Gradient: 5% B to 20% B in 7 min; Detector: UV 254 nm) to afford the title compound as a brown solid (36 mg, 75% yield). <sup>1</sup>H-NMR (DMSO, 400 MHz) δ(ppm): 11.41-10.87 (m, 2H), 9.17 (br s, 1H), 7.59-7.33 (m, 5H), 7.04-6.98 (m, 2H), 4.73 (s, 1H), 4.49-4.34 (m, 3H), 4.13-4.11 (m, 1H), 3.86-3.78 (m, 4H), 3.36-3.09 (m, 1H), 1.70-1.67 (m, 3H). MS: (ES, m/z): 343 [M+H]<sup>+</sup>.

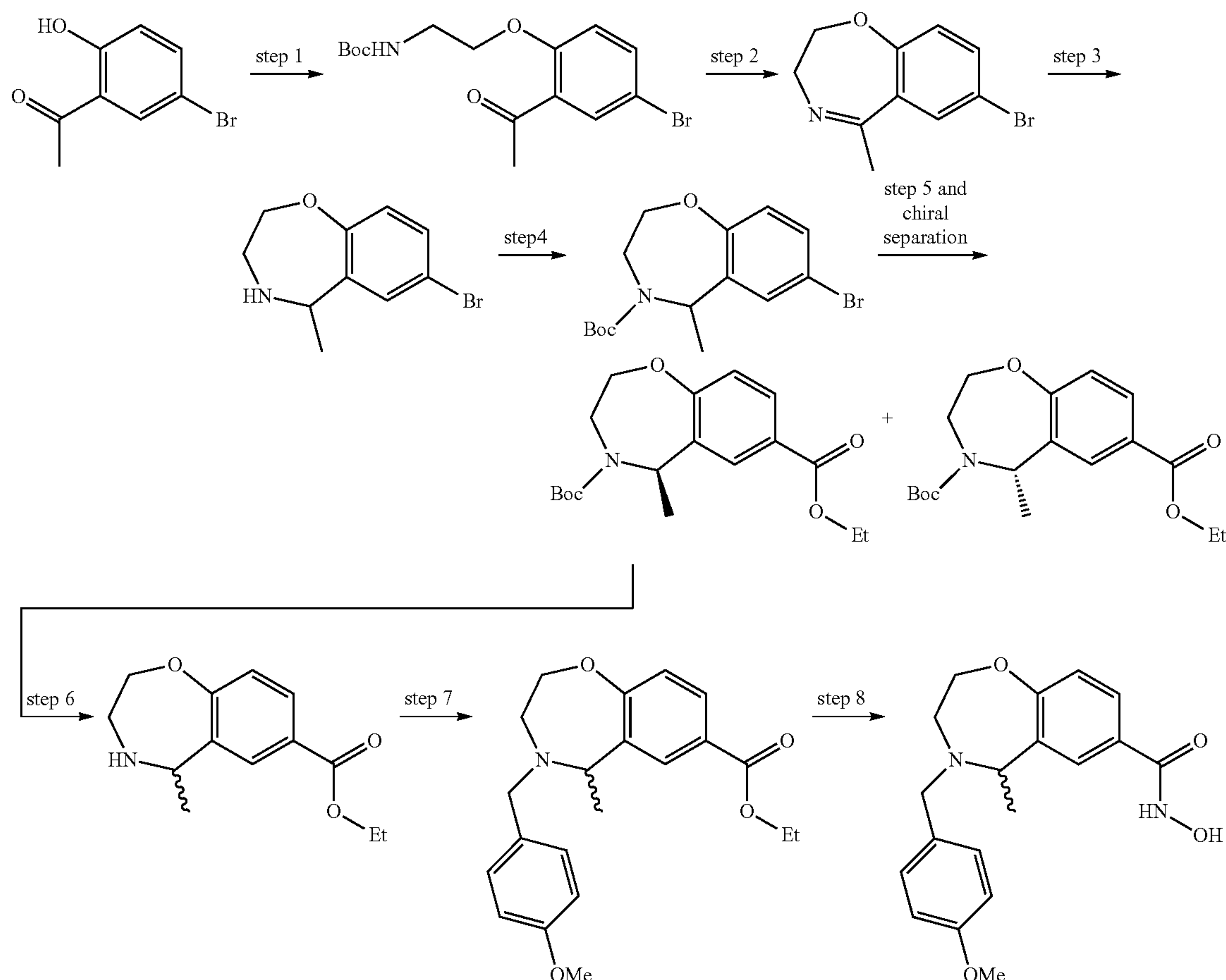
TABLE 29

The following compound was prepared according to the method of Example 59, using the second eluting isomer of the Step 5 product.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm)
	(ES, m/z): 343 [M + H] <sup>+</sup>	11.33-10.60 (m, 2H), 9.17-9.14 (m, 1H), 7.54-6.88 (m, 7H), 4.74-4.34 (m, 3H), 4.11-3.44 (m, 6H), 3.13-2.76 (m, 1H), 1.69-1.42 (m, 3H)

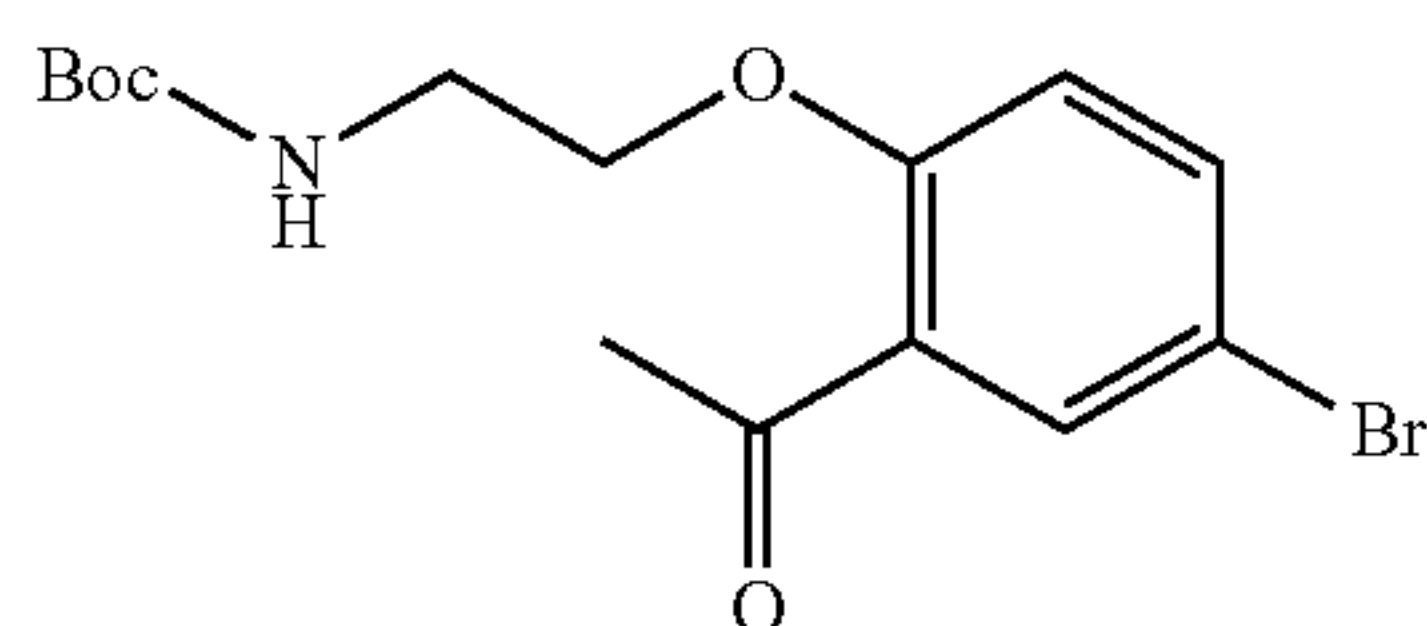
177

Example 60

Preparation of (R)—N-hydroxy-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo [f][1,4]oxazepine-7-carboxamide



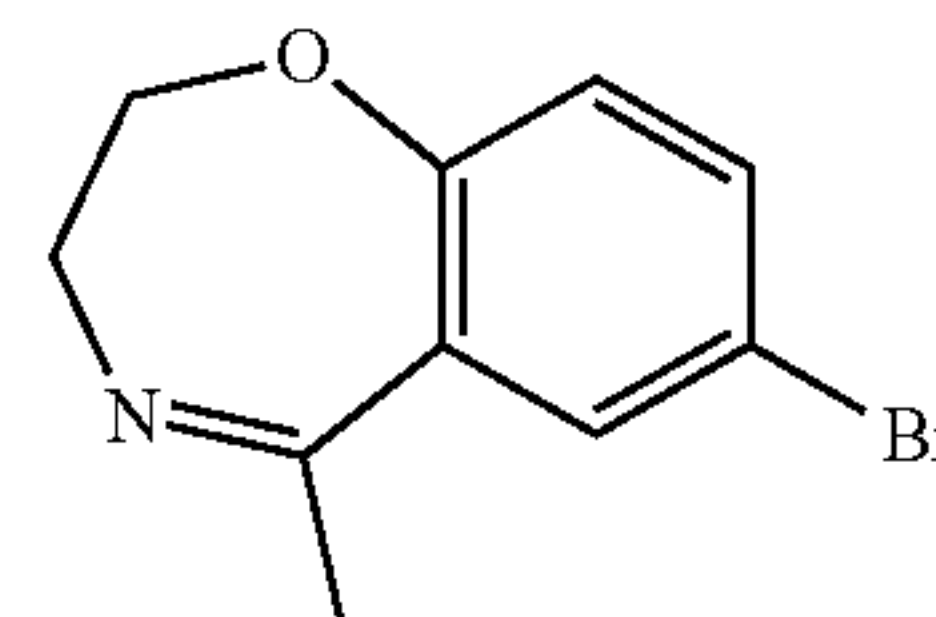
Step-1: tert-Butyl  
(2-(2-(4-bromophenoxy)ethyl)carbamate



Into a 500-mL 3-necked round-bottom flask, was placed a solution of 1-(5-bromo-2-hydroxyphenyl)ethan-1-one (30 g, 139.51 mmol, 1 equiv),  $K_2CO_3$  (29 g, 209.83 mmol, 3 equiv), potassium iodide (23.2 g, 1 equiv) and tert-butyl N-(2-bromoethyl)carbamate (37.5 g, 167.34 mmol, 1.2 equiv) in DMF (150 mL). The resulting solution was stirred overnight at 50° C. in an oil bath. The reaction mixture was cooled to 0° C. and quenched with  $H_2O$  (50 mL). The resulting solution was extracted with  $CH_2Cl_2$  (2×100 mL), washed with brine (5×100 mL) and dried over anhydrous  $Na_2SO_4$ . The solids were filtered out and the filtrate was concentrated under vacuum. The crude product was purified

by silica gel chromatography (Gradient 0-50% EtOAc/pet. ether over 50 min) to afford the title compound as a light yellow solid (39 g, 78% yield). MS: (ES, m/z): 358  $[M+H]^+$ .

Step-2: 7-Bromo-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine

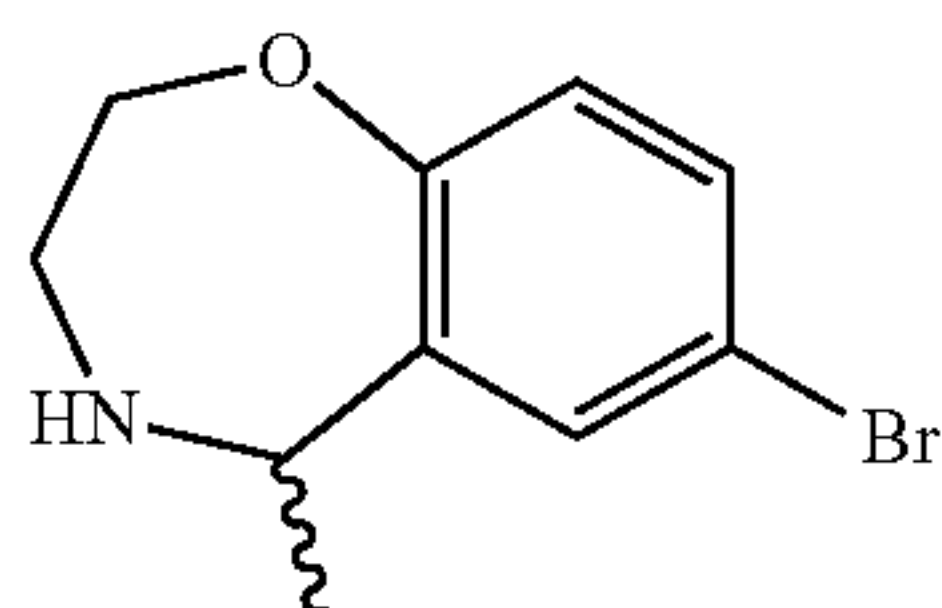


Into a 500-mL round-bottom flask, was placed tert-butyl N-[2-(2-(4-bromophenoxy)ethyl)carbamate (20 g, 55.83 mmol, 1 equiv),  $CH_2Cl_2$  (100 mL) and TFA (20 mL). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum to afford the title compound as a red solid (20 g) which was used without further purification. MS: (ES, m/z): 240  $[M+H]^+$ .



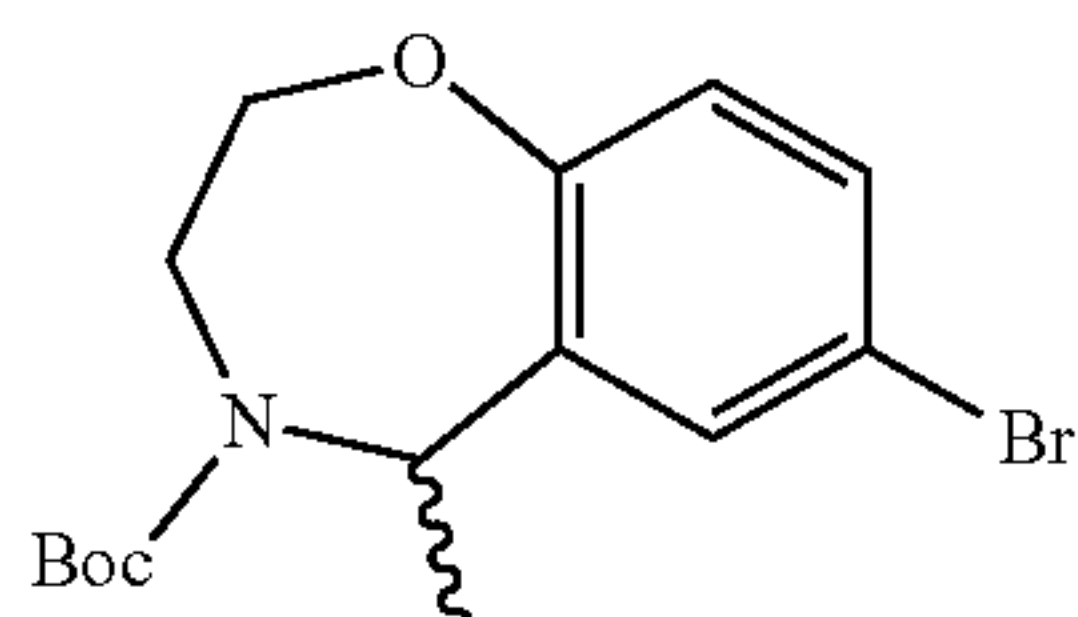
179

Step-3: 7-Bromo-5-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine



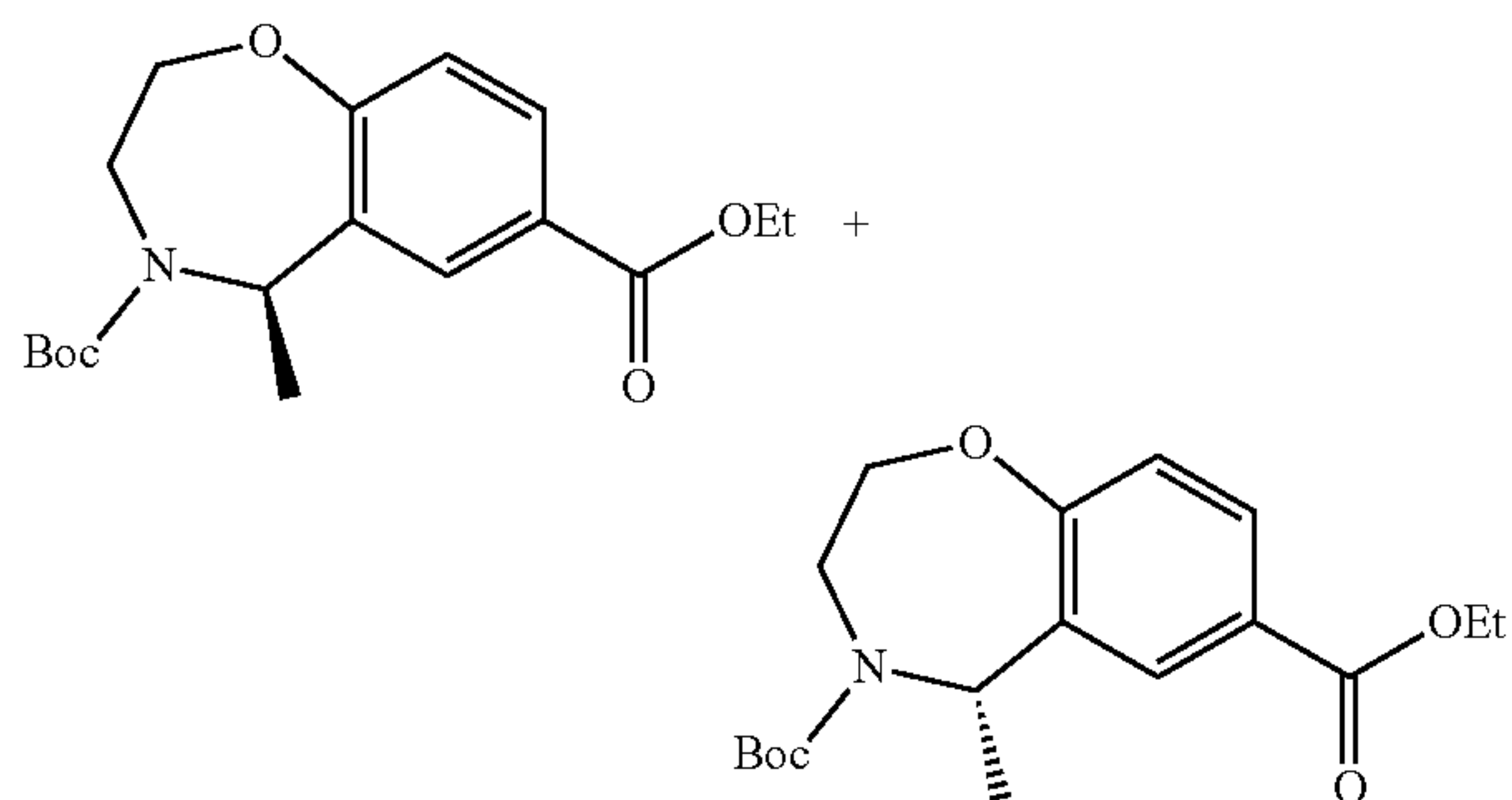
Into a 500-mL round-bottom flask, was placed a solution of 7-bromo-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine (10 g, 38.74 mmol, 1 equiv) in MeOH (100 mL), the pH value of the solution was adjusted to 7 with anhydrous sodium acetate at 0° C. Then Na(CN)BH<sub>3</sub> (7.9 g, 113.52 mmol, 3 equiv) was added at 0° C. The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum and 20 mL of water was added. The solids were collected by filtration to afford the title compound as a white solid (7 g, 75% yield) which was used without further purification. MS: (ES, m/z): 242 [M+H]<sup>+</sup>.

Step-4: tert-Butyl 7-bromo-5-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-4-carboxylate



Into a 50-mL round-bottom flask, was placed 7-bromo-5-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (2 g, 8.26 mmol, 1 equiv), CH<sub>2</sub>Cl<sub>2</sub> (20 mL), Et<sub>3</sub>N (2.51 g, 24.80 mmol, 3 equiv), di-tert-butyl dicarbonate (2.71 g, 12.42 mmol, 1.5 equiv). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The crude product was purified by silica gel chromatography (Gradient 0-30% EtOAc/pet. ether over 20 min) to afford the title compound as a light yellow oil (2.4 g, 85% yield). MS: (ES, m/z): 342 [M+H]<sup>+</sup>.

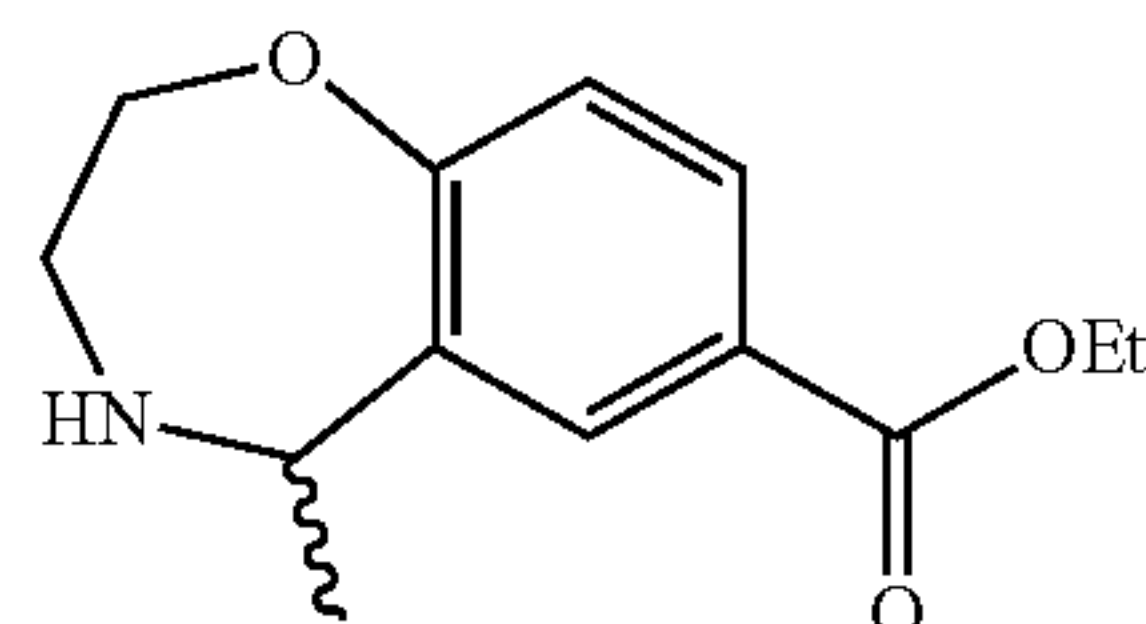
Step-5: 4-(tert-Butyl) 7-ethyl (R)-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,7(5H)-dicarboxylate



180

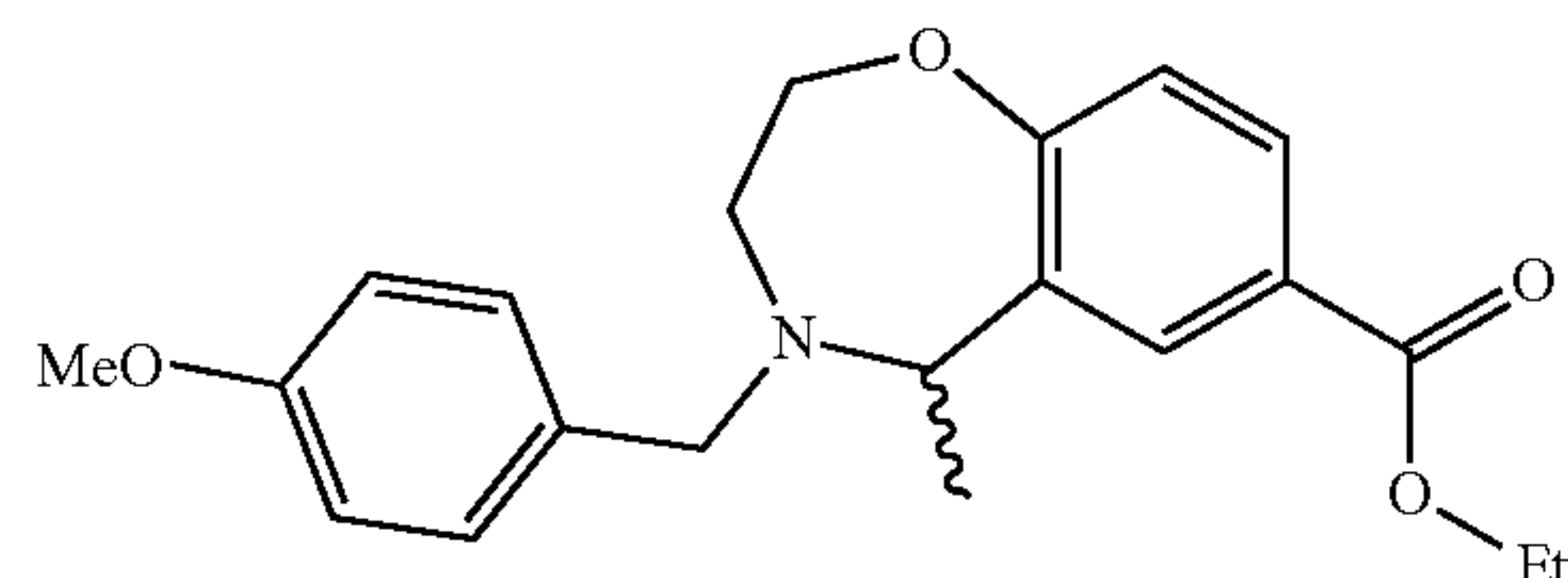
Into a 50-mL pressure tank reactor, was placed tert-butyl 7-bromo-5-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-4-carboxylate (2.4 g, 7.01 mmol, 1 equiv), ethanol (40 mL), Et<sub>3</sub>N (2.1 g, 20.75 mmol, 3 equiv), and Pd(dppf)Cl<sub>2</sub> (515.1 mg, 0.70 mmol, 0.1 equiv). CO (g) (60 atm) was introduced and the resulting solution was stirred overnight at 120° C. The solids were filtered out and the filtrate was concentrated under vacuum and purified by silica gel chromatography (Gradient 0-10% EtOAc/pet. ether over 30 min) to afford the racemic mixture of the title compounds, which were separated by Prep-SFC (Column Chiralpak IC OBD, 5 μm, 5×250 mm; Mobile Phase: 75% CO<sub>2</sub>, 25% Isopropanol; Flow rate: 170 mL/min; Detector, UV 254, 220 nm) to afford the single isomers of the title compounds as light yellow oils (first eluting isomer: 440 mg, 19% yield; second eluting isomer: 500 mg, 21% yield). MS: (ES, m/z): 336 [M+H]<sup>+</sup>.

Step-6: Ethyl (R)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate



Into a 50-mL round-bottom flask, was placed the first eluting isomer from Step 5 (4-(tert-butyl) 7-ethyl (R)-5-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,7(5H)-dicarboxylate) (440 mg, 1.31 mmol, 1 equiv), CH<sub>2</sub>Cl<sub>2</sub> (5 mL), and TFA (2 mL). The resulting solution was stirred overnight at room temperature and concentrated under vacuum. The crude product was purified by silica gel chromatography (Gradient 10-50% EtOAc/pet. ether over 30 min) to afford the title compound as a light yellow oil (300 mg, 97% yield). MS: (ES, m/z): 236 [M+H]<sup>+</sup>.

Step-7: Ethyl (R)-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate

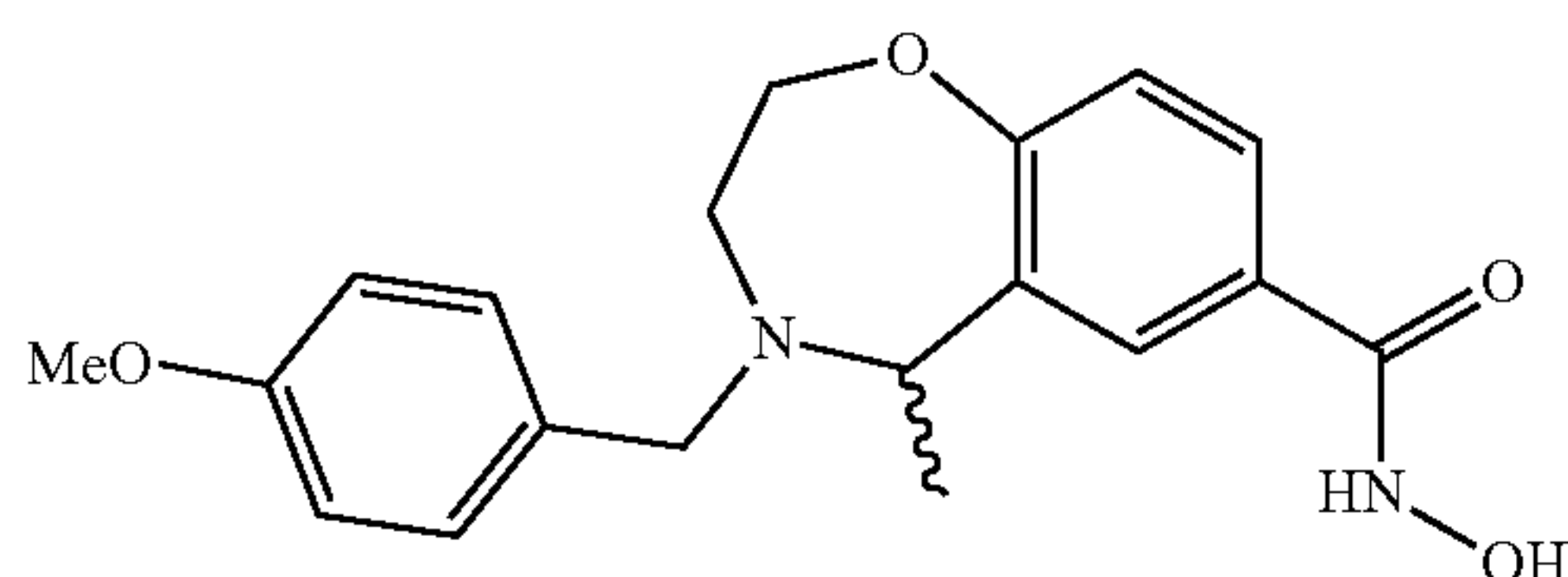


Into a 50-mL round-bottom flask, was placed 4-methoxybenzaldehyde (57.8 mg, 0.42 mmol, 1 equiv), MeOH (2 mL), and ethyl (R)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate (100 mg, 0.43 mmol, 1 equiv). The mixture was stirred for 30 min at room temperature, and then Na(CN)BH<sub>3</sub> (80.4 mg, 1.28 mmol, 3 equiv) was added at 0° C. The resulting solution was stirred overnight at room temperature. The reaction was then quenched with H<sub>2</sub>O (2 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5×10 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (EtOAc/pet. ether,

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1:3) to afford the title compounds as a light yellow oil (80 mg, 53% yield). MS: (ES, m/z): 356 [M+H]<sup>+</sup>.

Step-8: (R)—N-Hydroxy-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide



Into a 25-mL round-bottom flask, was placed ethyl (R)-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate (80 mg, 0.23 mmol, 1 equiv), THF/MeOH (1.5 mL, 4:1). This was followed by the addition of NH<sub>2</sub>OH (50% in water, 913 mg, 60 equiv) and aq. 1N NaOH (0.46 mL, 2 equiv). The resulting solution was stirred for 2 days at room temperature. The crude product was purified by Prep-HPLC (Column: Atlantis T3 C18 OBD, 5 μm, 19×150 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN; Flow rate: 25 mL/min; Gradient: 10% B to 40% B in 10 min; Detector, UV 254, 220 nm) to afford the title compound as an off-white solid (12 mg, 11% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.24 (s, 1H), 10.20-10.13 (br s, 1H), 9.13-9.09 (br s, 1H), 7.83-7.76 (br s, 2H), 7.49-7.41 (m, 2H), 7.24-7 (m, 3H), 4.84-4.69 (m, 1H), 4.60-3.79 (m, 5H), 3.79 (s, 3H), 3.40-3 (m, 1H), 1.69-1.55 (m, 3H). MS: (ES, m/z): 343 [M+H]<sup>+</sup>.

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## Example 61

Preparation of N8-hydroxy-N4-(4-methoxyphenyl)-2,3-dihydropyrido[2,3-f][1,4]oxazepine-4,8(5H)-dicarboxamide

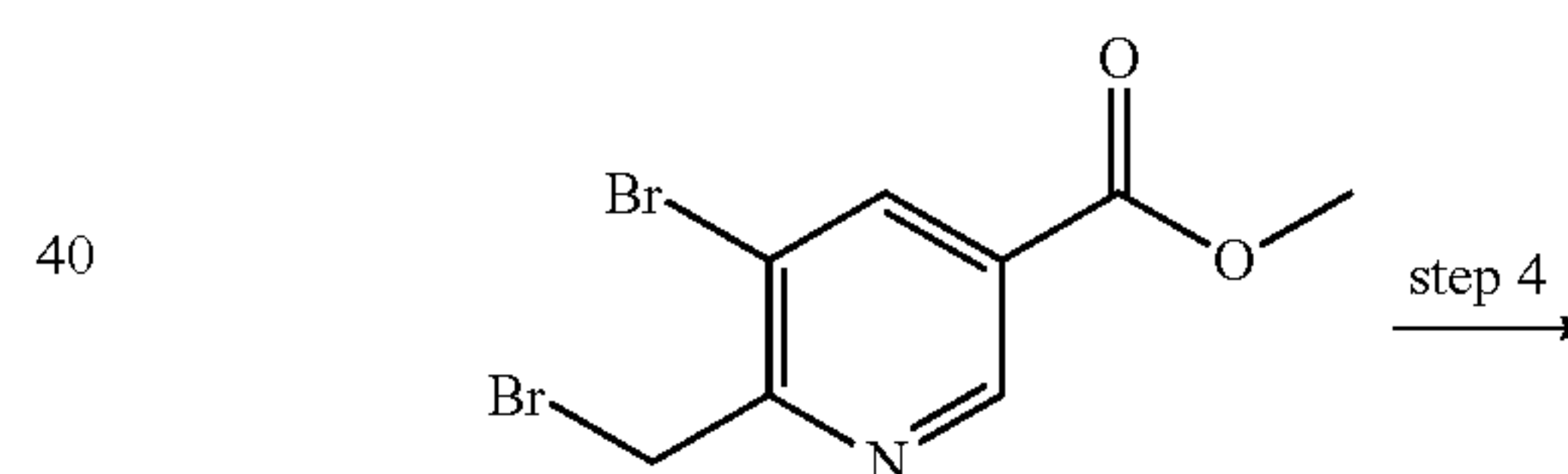
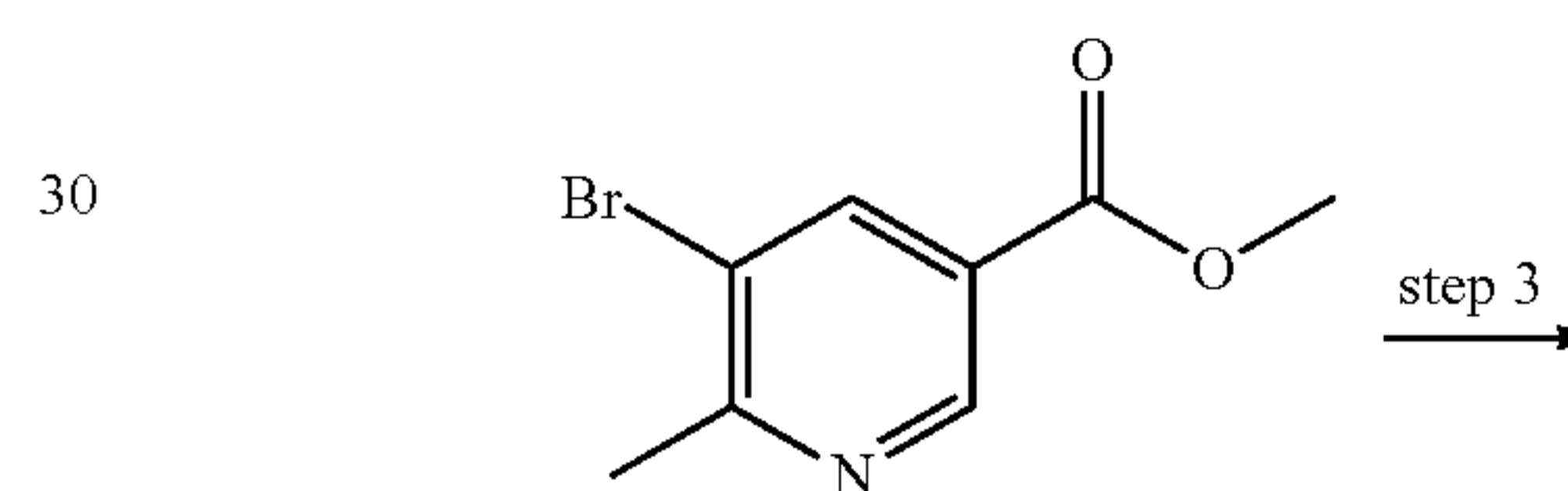
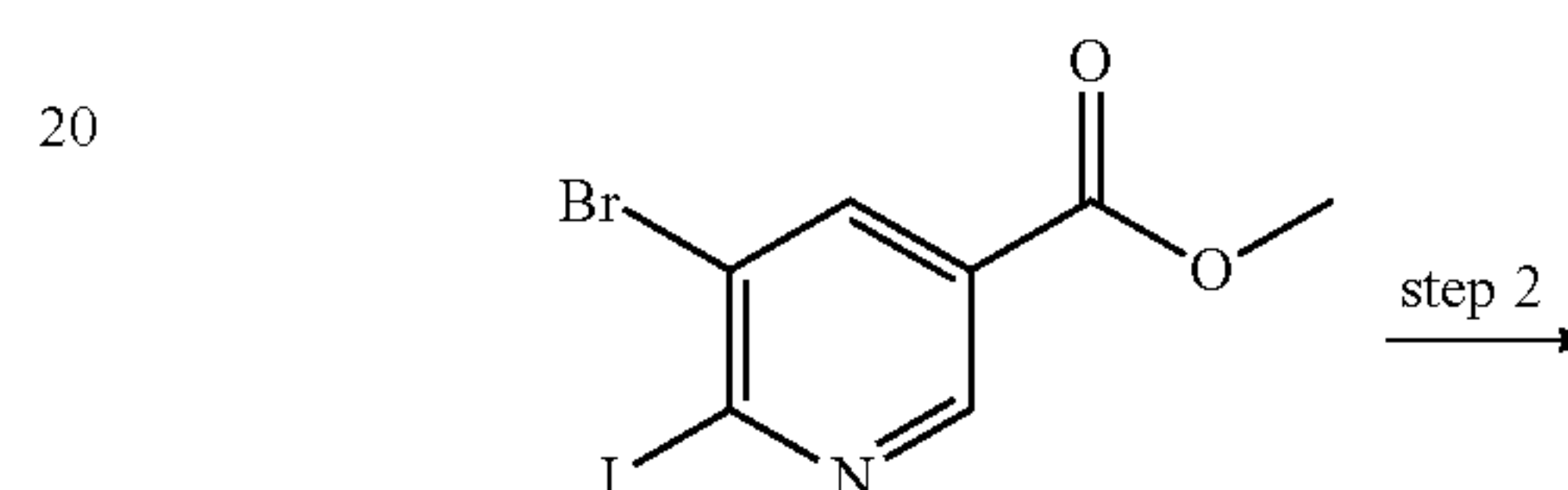
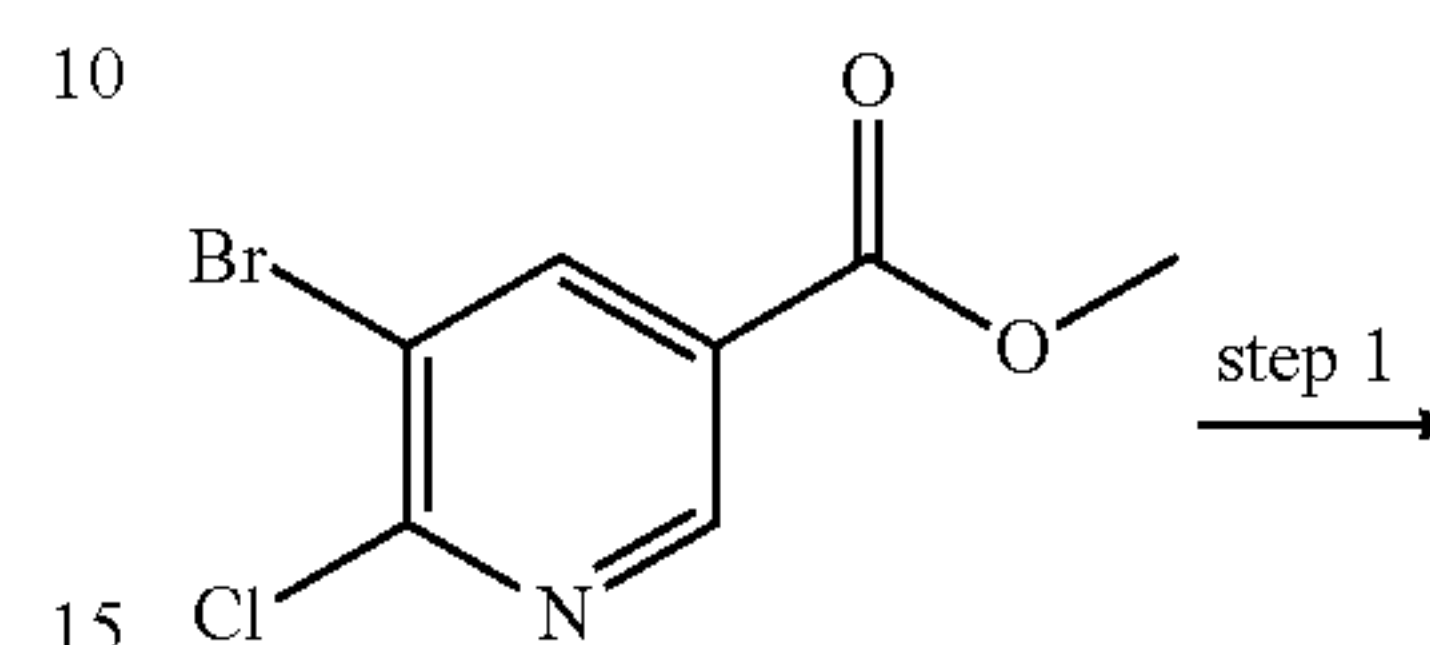


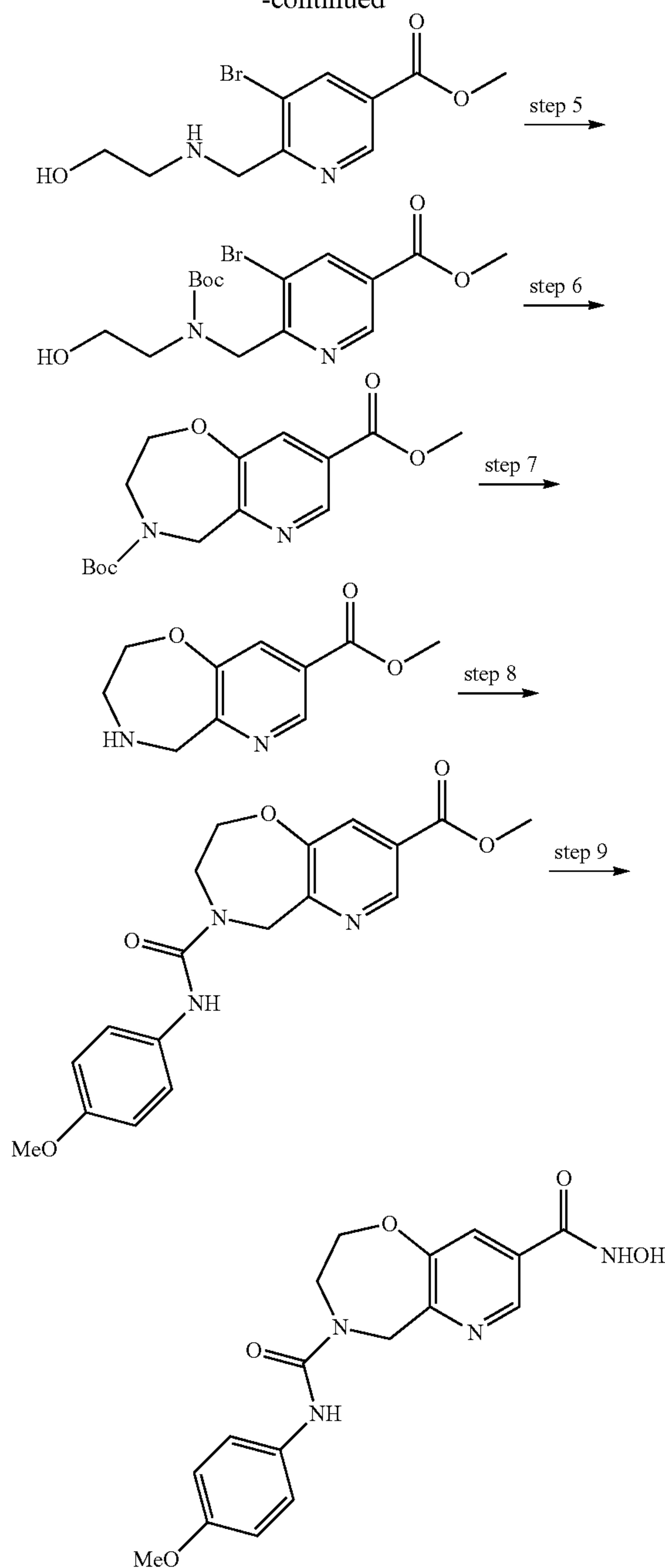
TABLE 30

The following compounds were prepared according to the method of Example 60, using the second eluting isomer of the Step 5 product.		
Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ(ppm)
	(ES, m/z): 343 [M + H] <sup>+</sup>	11.24 (s, 1H), 10.23-10.12 (br s, 1H), 9.13-9.04 (br s, 1H), 7.76 (s, 2H), 7.50-7.42 (m, 2H), 7.17-7.04 (m, 3H), 4.83 (br, 1H), 4.48-4 (m, 5H), 3.78 (s, 3H), 3.34-3.05 (m, 1H), 1.68-1.53 (m, 3H)
(R)/(S) isomer		

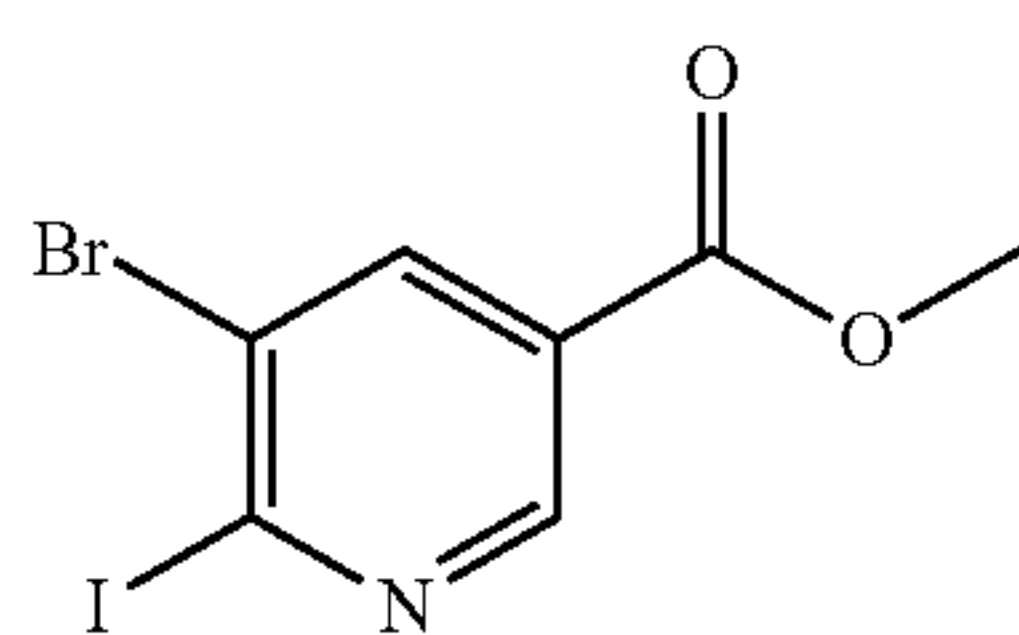


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-continued



Step-1: Methyl  
5-bromo-6-iodopyridine-3-carboxylate

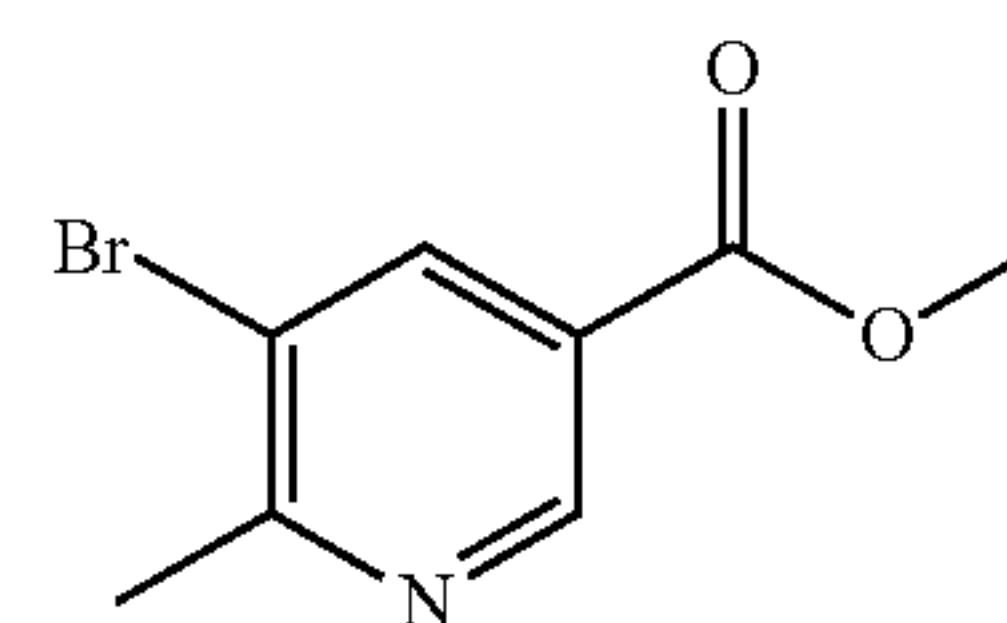


Into a 1000-mL round-bottom flask, was placed methyl 5-bromo-6-chloropyridine-3-carboxylate (11 g, 43.92 mmol, 1 equiv), MeCN (330 mL), trimethylsilyl iodide

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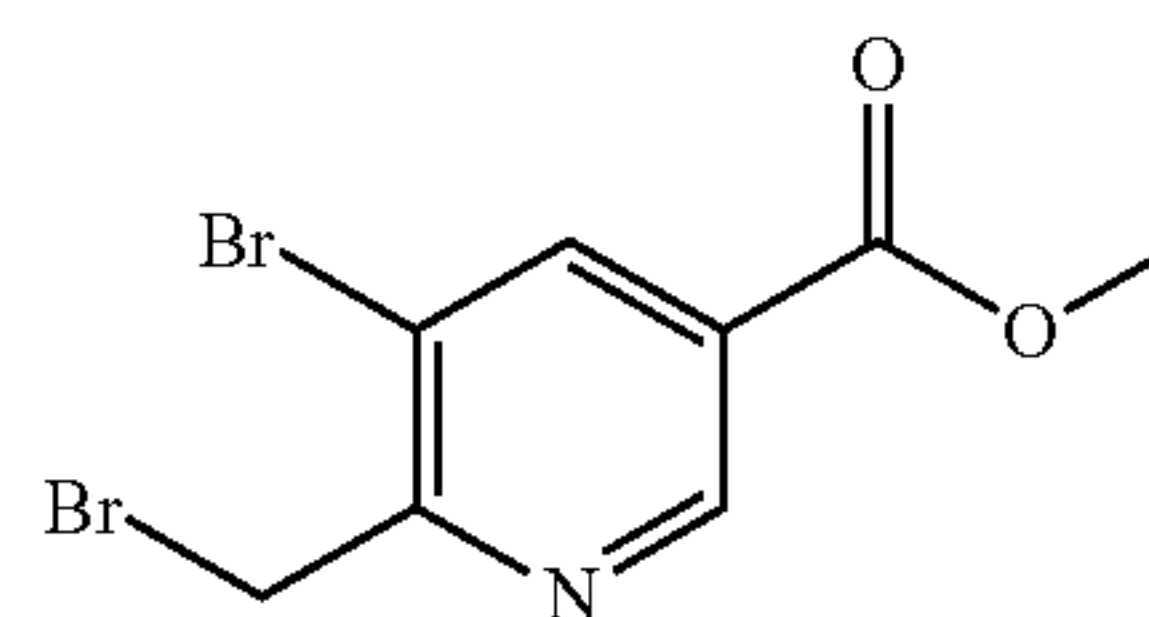
(8.767 g, 1 equiv) and sodium iodide (19.7 g, 3 equiv). The resulting mixture was stirred for 4 h at 25° C. and then concentrated. The residue was diluted with H<sub>2</sub>O (300 mL). The pH value of the solution was adjusted to 7 with 2N NaOH. The solids were collected by filtration to afford the title compound as a yellow solid (16 g) which was used without further purification. MS: (ES, m/z): 250 [M+H]<sup>+</sup>.

Step-2: Methyl  
5-bromo-6-methylpyridine-3-carboxylate



Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed methyl 5-bromo-6-iodopyridine-3-carboxylate (6 g, 17.55 mmol, 1 equiv), 1,4-dioxane (60 mL), trimethyl-1,3,5,2,4,6-trioxatriborinane (15 mL, 50% in THF, 3 equiv), Pd(dppf) Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (1.44 g, 0.1 equiv) and potassium carbonate (7.34 g, 53.10 mmol, 3 equiv). The resulting solution was stirred for 72 h at 75° C. in an oil bath. The reaction mixture was cooled to room temperature. The solids were filtered out. The filtrate was diluted with EtOAc (100 mL), washed with brine (3×30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:10) to afford the title compound as an off-white solid (3 g, 74% yield). MS: (ES, m/z): 230 [M+H]<sup>+</sup>.

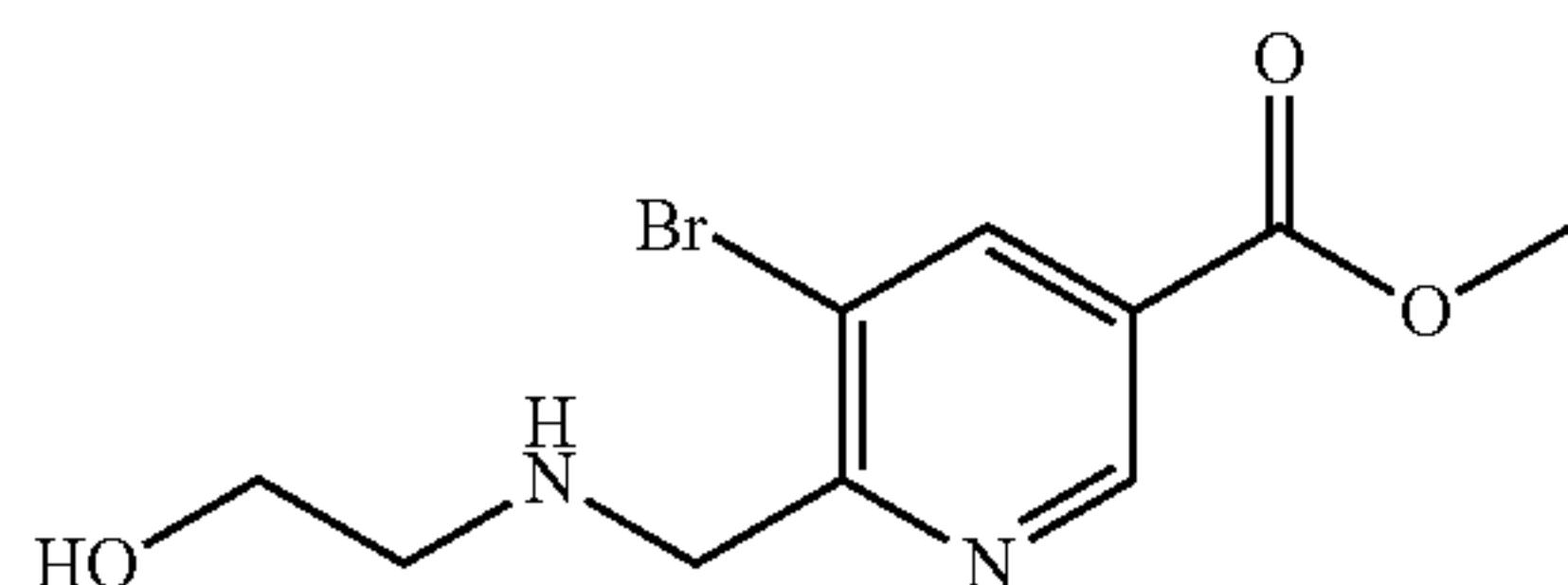
Step-3: Methyl  
5-bromo-6-(bromomethyl)pyridine-3-carboxylate



Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed methyl 5-bromo-6-methylpyridine-3-carboxylate (3 g, 13.04 mmol, 1 equiv), CCl<sub>4</sub> (60 mL), NBS (2.435 g, 13.68 mmol, 1.05 equiv) and benzoyl peroxide (158 mg, 0.62 mmol, 0.05 equiv). The resulting mixture was stirred for 16 h at 80° C. in an oil bath. The reaction mixture was cooled to room temperature. The solids were filtered out. The filtrate was concentrated and diluted with EtOAc (150 mL), washed with brine (3×50 mL). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford the title compound as a brown oil (2.5 g) which was used without further purification. MS: (ES, m/z): 310 [M+H]<sup>+</sup>.

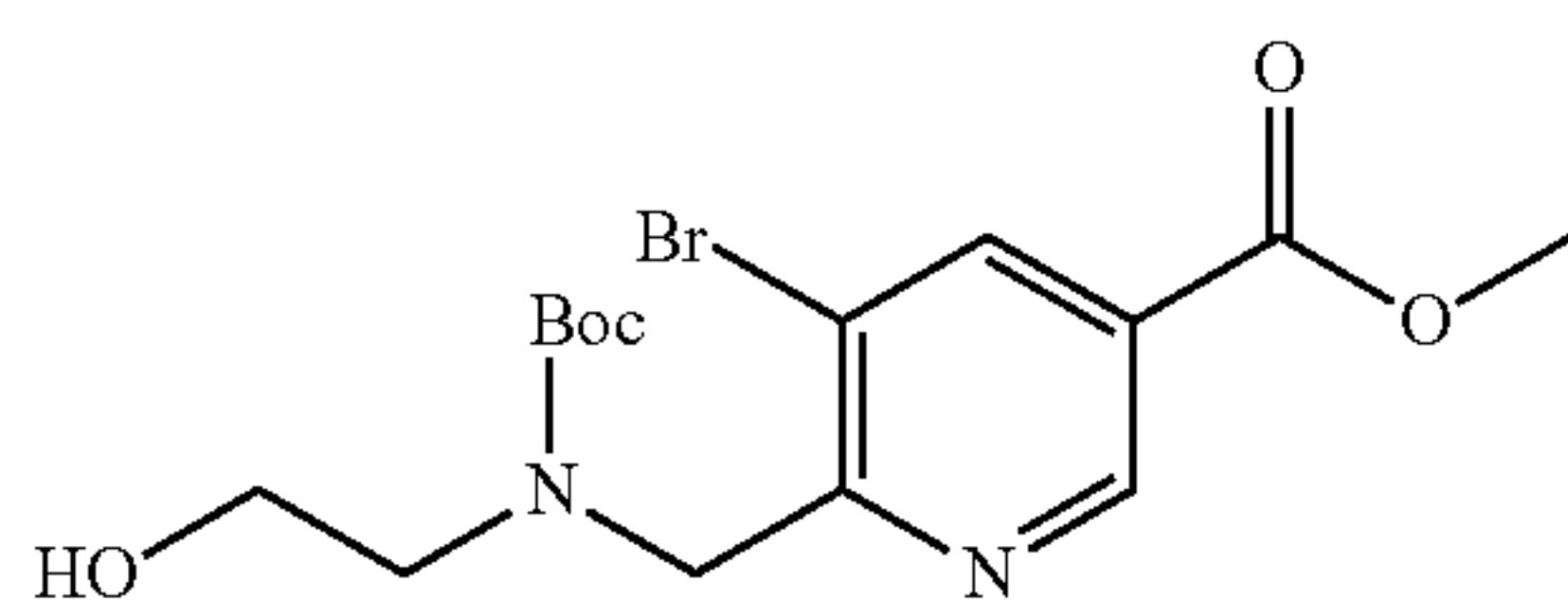
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Step-4: Methyl 5-bromo-6-[[[(2-hydroxyethyl)amino]methyl]pyridine-3-carboxylate



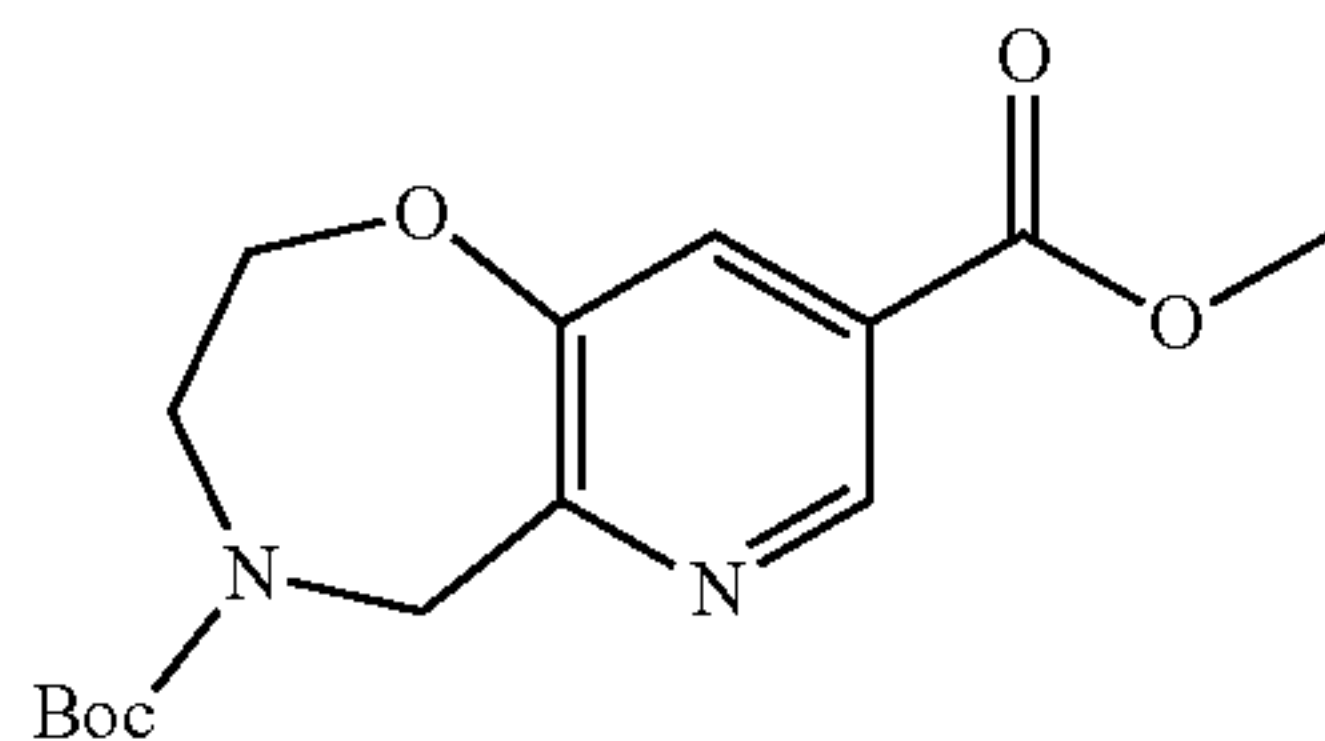
Into a 250-mL round-bottom flask, was placed MeCN (50 mL), 2-aminoethan-1-ol (990 mg, 16.21 mmol, 2 equiv) and potassium carbonate (2.26 g, 16.32 mmol, 2 equiv). This was followed by the addition of a solution of methyl 5-bromo-6-(bromomethyl)pyridine-3-carboxylate (2.5 g, 4.86 mmol, 1 equiv) in MeCN (20 mL) dropwise with stirring at 0° C. The resulting solution was stirred for additional 2 h at 0° C. The solids were filtered out. The filtrate was concentrated. The residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 20:1) to afford the title compound as a yellow solid (0.7 g, 50% yield). MS: (ES, m/z): 289 [M+H]<sup>+</sup>.

Step-5: Methyl 5-bromo-6-(((tert-butoxycarbonyl)(2-hydroxyethyl)amino)methyl)nicotinate



Into a 25-mL round-bottom flask, was placed methyl 5-bromo-6-[[[(2-hydroxyethyl)amino]methyl]pyridine-3-carboxylate (500 mg, 1.73 mmol, 1 equiv), THF (10 mL), di-tert-butyl dicarbonate (416 mg, 1.91 mmol, 1.10 equiv), and Et<sub>3</sub>N (350 mg, 3.47 mmol, 2 equiv). The resulting mixture was stirred for 1 h at 25° C. and then concentrated. The residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a yellow-green oil (0.55 g, 82% yield). MS: (ES, m/z): 389 [M+H]<sup>+</sup>.

Step-6: 4-(tert-Butyl) 8-methyl 2,3-dihydropyrido[2,3-f][1,4]oxazepine-4,8(5H)-dicarboxylate

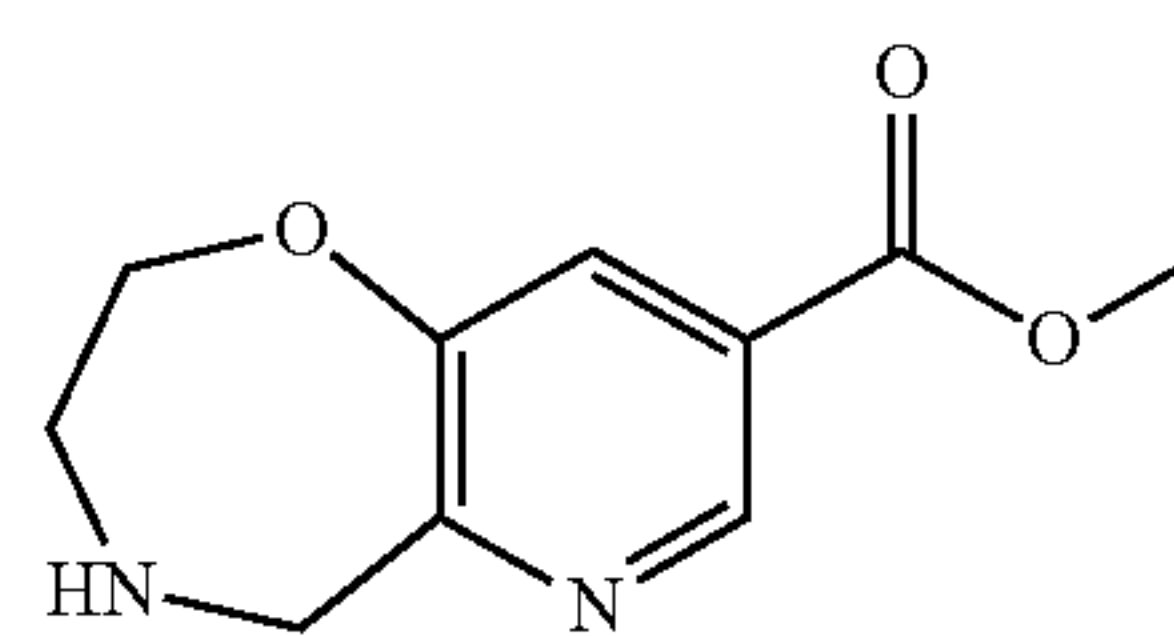


Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed Pd(OAc)<sub>2</sub> (87 mg, 0.39 mmol, 0.05 equiv), Johnphos (0.184 g, 0.08 equiv), Cs<sub>2</sub>CO<sub>3</sub> (3.784 g, 11.61 mmol, 1.5 equiv) and 1,4-dioxane (30 mL). This was followed by the addition of a solution of methyl 5-bromo-6-(((tert-butoxycarbonyl)(2-

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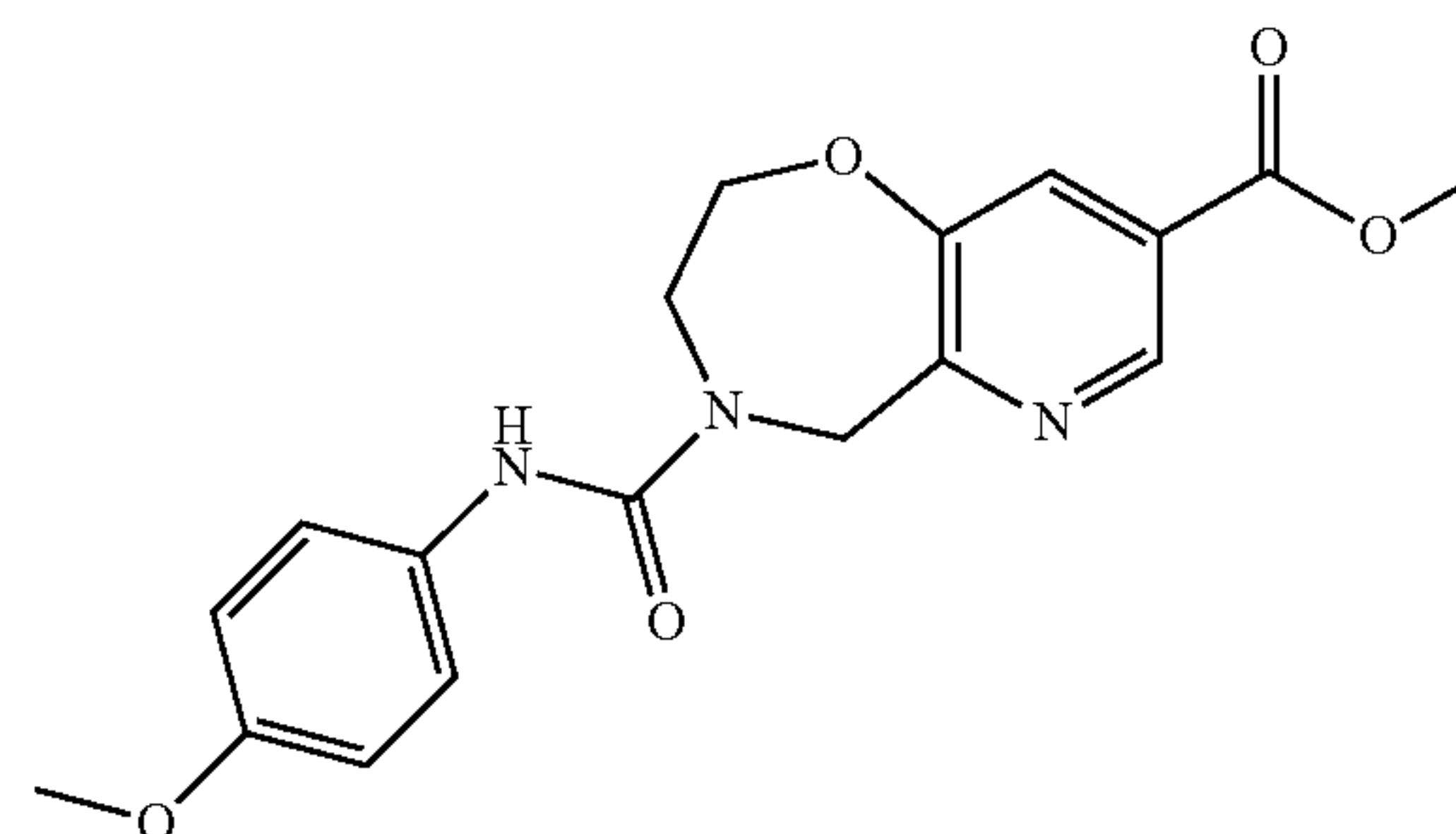
hydroxyethyl)amino)methyl)nicotinate (3 g, 7.71 mmol, 1 equiv) in 1,4-dioxane (20 mL). The resulting mixture was stirred for 16 h at 95° C. in an oil bath. The reaction mixture was cooled to room temperature and diluted with EtOAc (50 mL) and H<sub>2</sub>O (50 mL). The resulting solution was washed with brine (3×50 mL). The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 20:1) to afford the title compound as an orange solid (1.2 g, 50% yield). MS: (ES, m/z): 309 [M+H]<sup>+</sup>.

Step-7: Methyl 2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxylate



Into a 100-mL round-bottom flask, was placed 4-(tert-butyl) 8-methyl 2,3-dihydropyrido[2,3-f][1,4]oxazepine-4,8(5H)-dicarboxylate (1.2 g, 3.89 mmol, 1 equiv), CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and TFA (5 mL). The resulting solution was stirred for 2 h at 25° C. The pH value of the solution was adjusted to 7-8 with NaHCO<sub>3</sub>. The solution was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 10:1) to afford the title compound as an orange solid (0.6 g, 74% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 8.88 (s, 1H), 7.90 (s, 1H), 4.23 (s, 2H), 4.12-4.08 (t, 2H), 3.94 (s, 3H), 3.30-3.17 (t, 2H). MS: (ES, m/z): 209 [M+H]<sup>+</sup>.

Step-8: Methyl 4-((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxylate

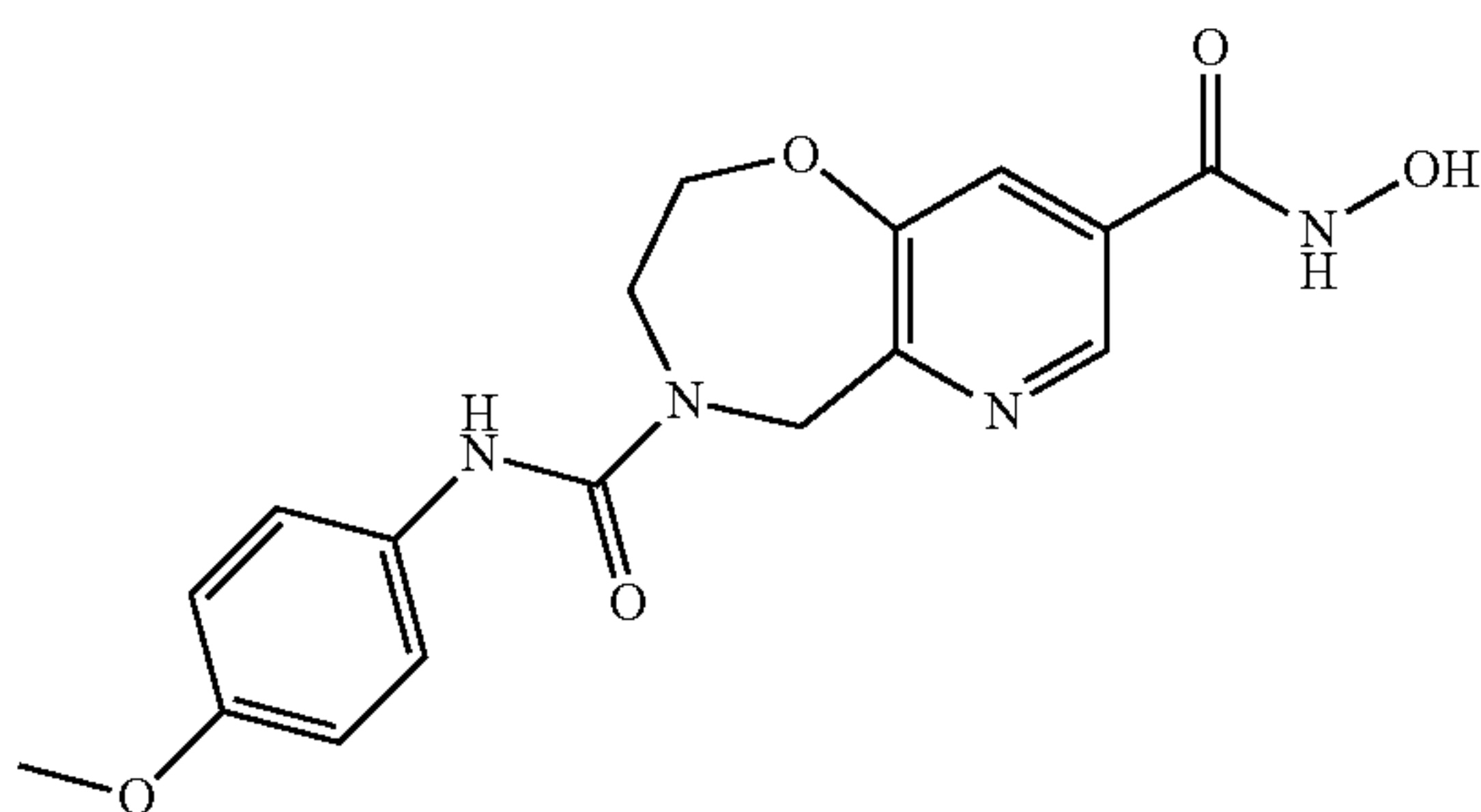


Into a 10-mL round-bottom flask, was placed methyl 2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxylate (50 mg, 0.24 mmol, 1 equiv), 1-isocyanato-4-methoxybenzene (43 mg, 0.29 mmol, 1.2 equiv), Et<sub>3</sub>N (73 mg, 0.72 mmol, 3 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (3 mL). The resulting mixture was stirred for 3 h at 25° C. and concentrated under vacuum. The residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 20:1) to afford the title compound as a yellow oil (60 mg, 70% yield). MS: (ES, m/z): 358 [M+H]<sup>+</sup>.



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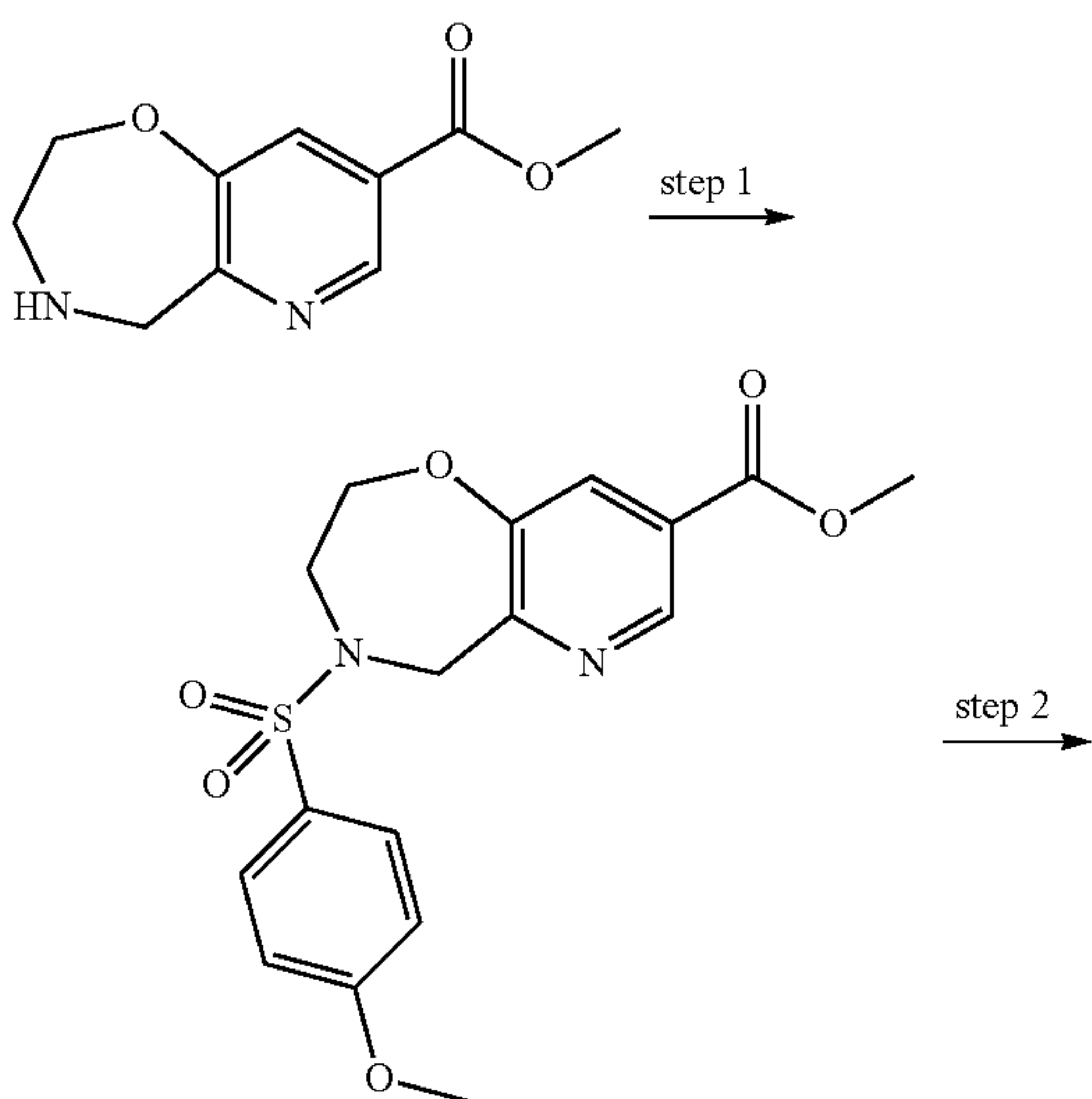
Step-9: 8-N-Hydroxy-4-N-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-4,8-dicarboxamide



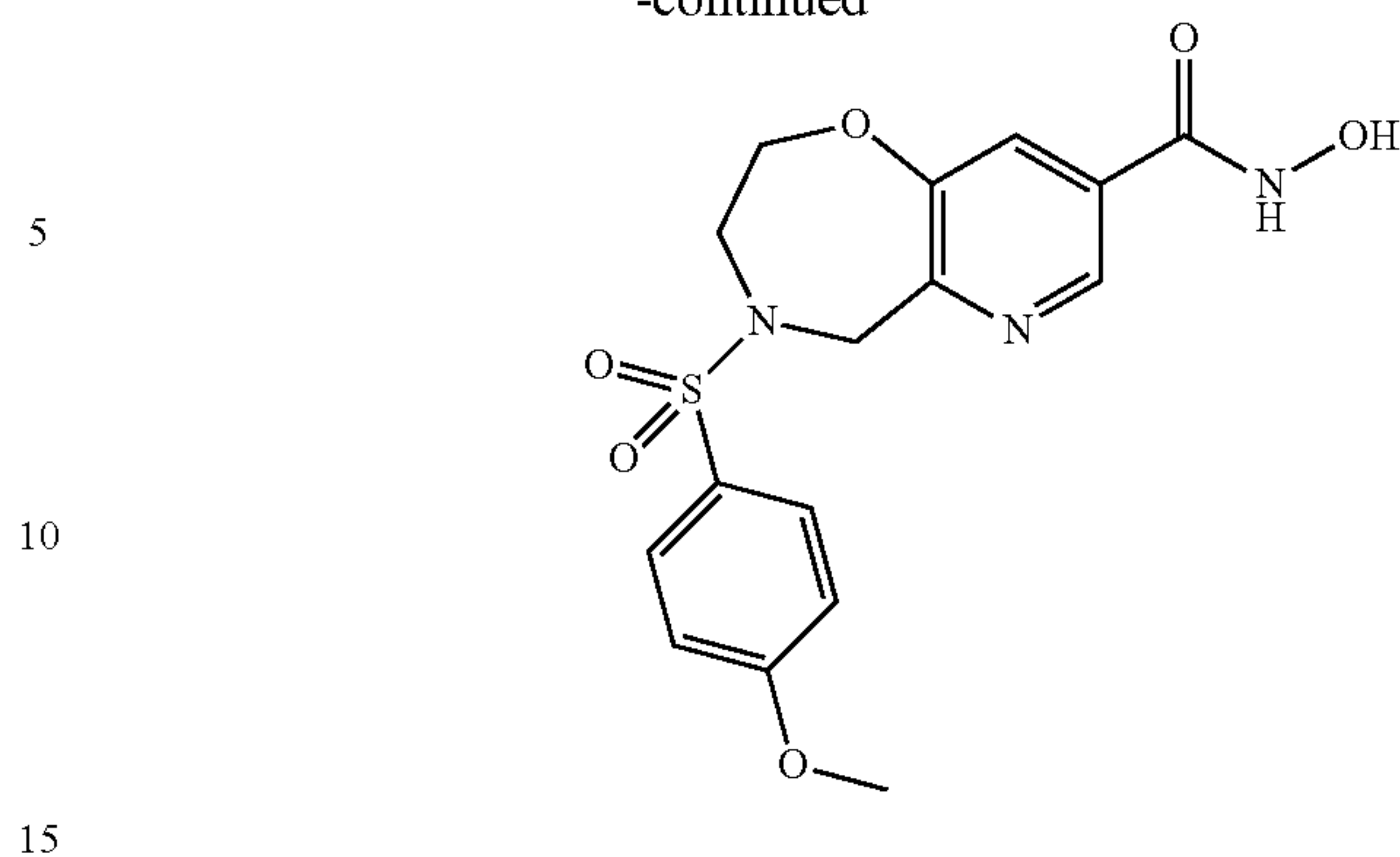
Into a 25-mL round-bottom flask, was placed methyl 4-((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydropyrido [2,3-f][1,4]oxazepine-8-carboxylate (60 mg, 0.17 mmol, 1 equiv), aq. 1N NaOH (0.34 mL, 2 equiv), NH<sub>2</sub>OH (50% in water, 0.33 g, 30 equiv), THF/MeOH (4:1, 2 mL). The resulting solution was stirred for 1 h at 25° C. The pH value of the solution was adjusted to 6 with 1N HCl. The crude product was purified by Prep-HPLC (Column HSS C18 OBD, 1.8 μm, 2.1×50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 23% B in 6 min, hold 1 min; Detector, UV 254, 220 nm) to afford the title compound as an off-white solid (31 mg, 52% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.35 (s, 1H), 8.45-8.51 (t, 2H), 7.61-7.62 (d, 1H), 7.25-7.28 (m, 2H), 6.78-6.82 (m, 2H), 4.88-4.94 (d, 2H), 4.31-4.32 (d, 2H), 3.88-3.92 (d, 2H), 3.68-3.74 (d, 3H). MS: (ES, m/z): 359 [M+H]<sup>+</sup>.

**Example 62**

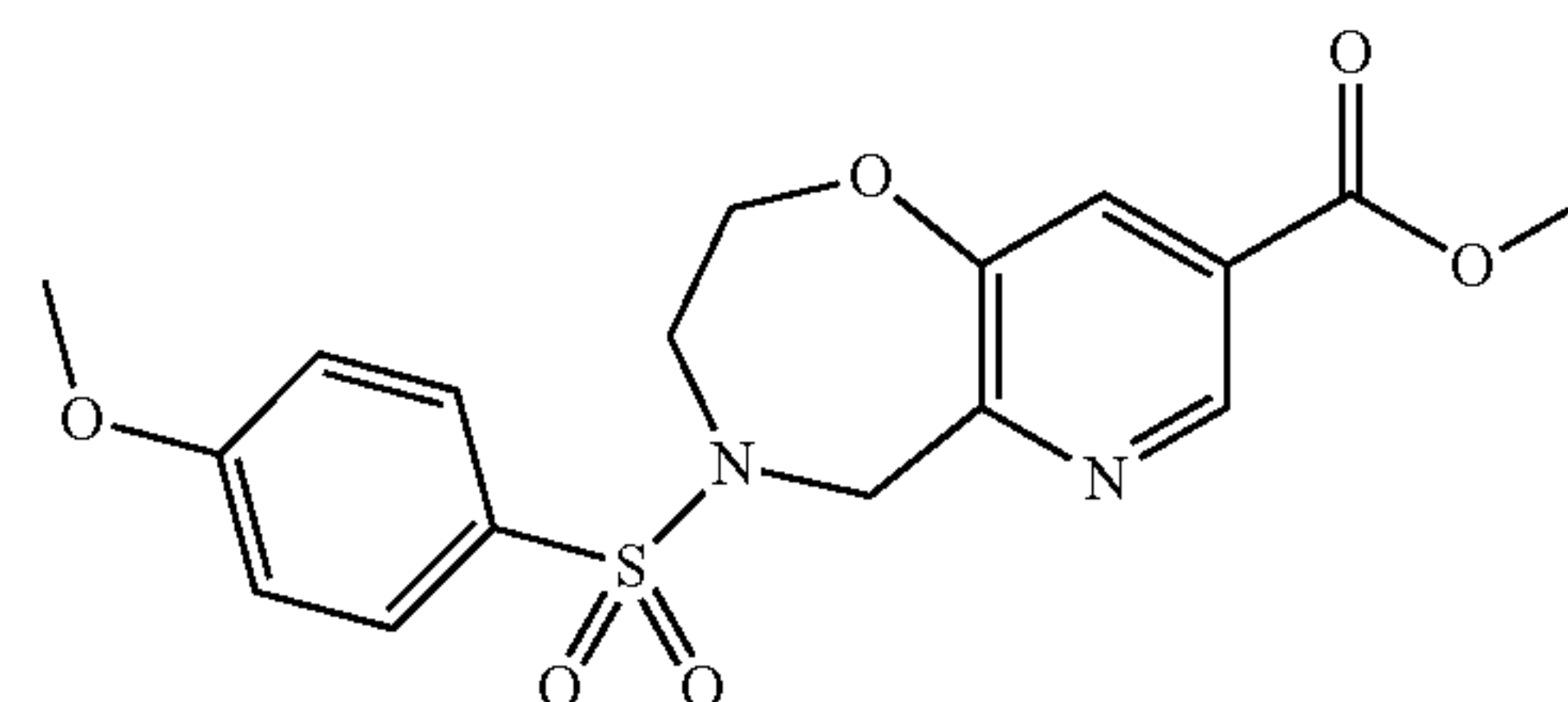
Preparation of N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxamide

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-continued

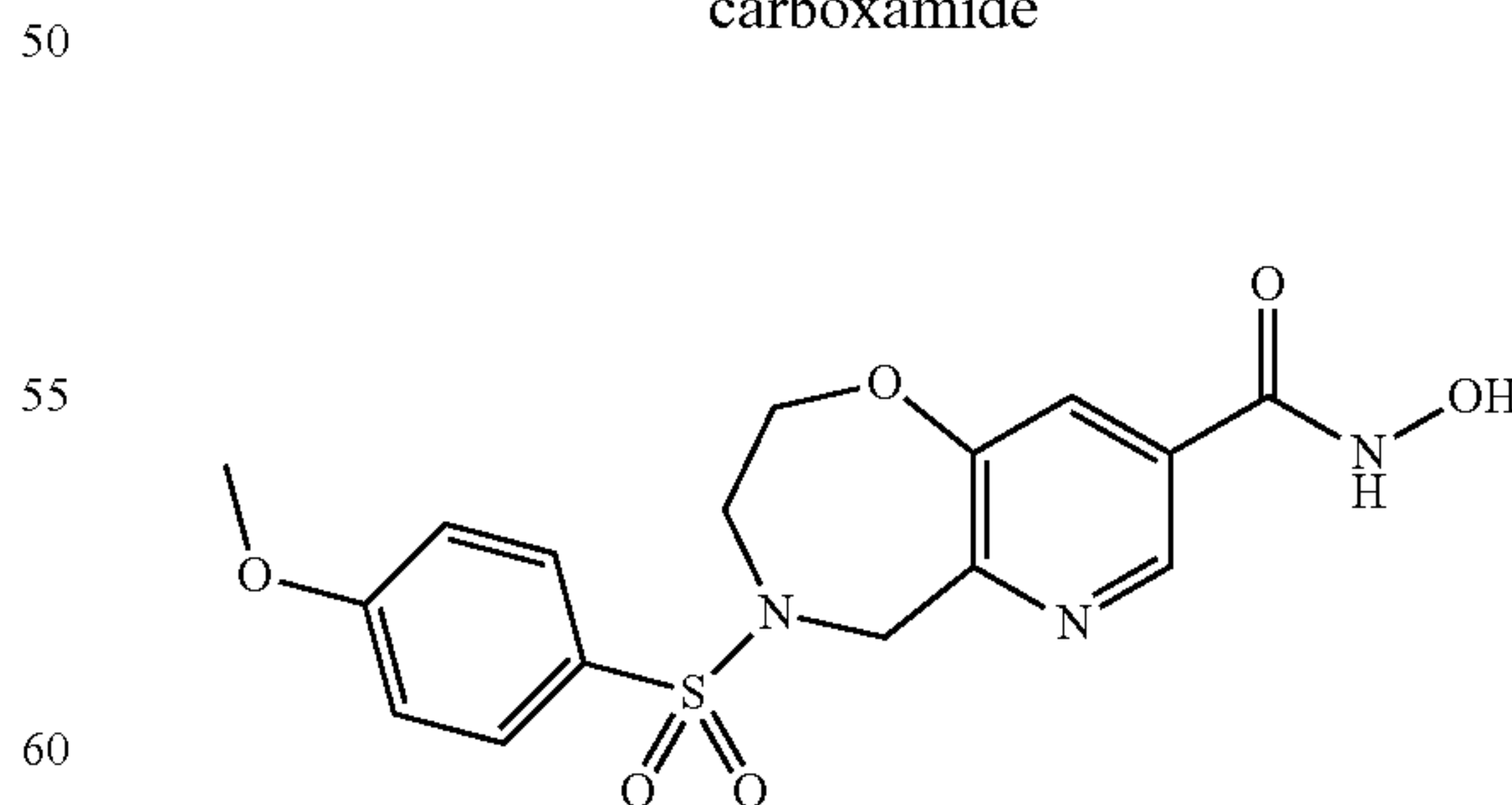


Step-1: Methyl 4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxylate



Into a 10-mL round-bottom flask, was placed methyl 2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxylate (100 mg, 0.48 mmol, 1 equiv), 4-methoxybenzene-1-sulfonyl chloride (249 mg, 1.20 mmol, 2.5 equiv), 4-dimethylaminopyridine (29 mg, 0.24 mmol, 0.5 equiv), Et<sub>3</sub>N (146 mg, 1.44 mmol, 3 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (3 mL). The resulting mixture was stirred for 3 h at 25° C. The reaction was then quenched by the addition of NH<sub>4</sub>Cl. The resulting solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×10 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 20:1) to afford the title compound as a yellow solid (100 mg, 55% yield). MS: (ES, m/z): 379 [M+H]<sup>+</sup>.

Step-2: N-Hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxamide



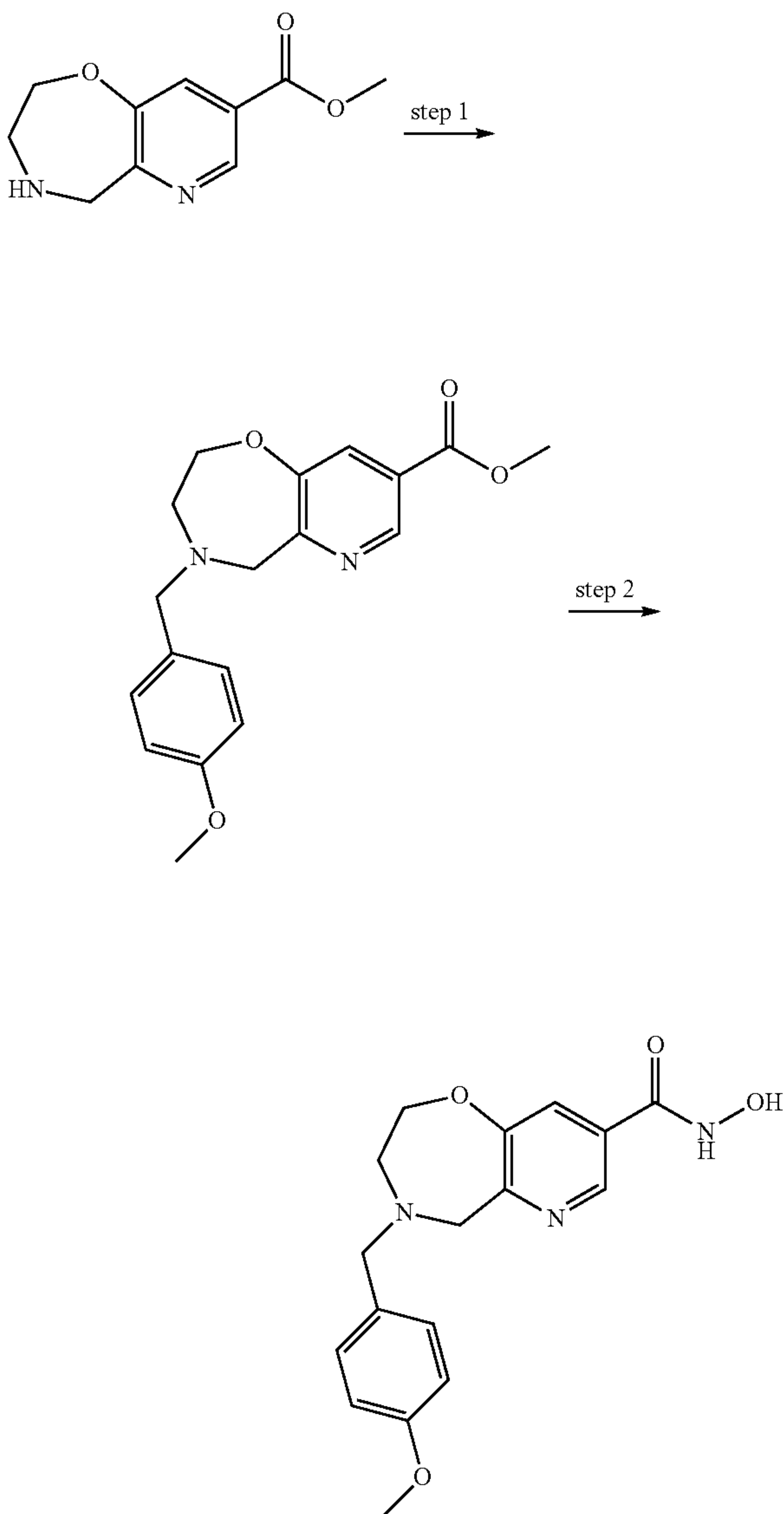
Into a 25-mL round-bottom flask, was placed methyl 4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxylate (110 mg, 0.29 mmol, 1 equiv), aq. 1N NaOH (0.58 mL, 2 equiv), and NH<sub>2</sub>OH (50% in water, 0.57 g, 30 equiv), THF/MeOH (4:2, 2 mL). The

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resulting solution was stirred for 1 h at 25° C. The pH value of the solution was adjusted to 6 with 1N HCl. The crude product was purified by Prep-HPLC (Column: HSS C18 OBD, 1.8  $\mu$ m, 2.1×50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 23% B in 6 min, hold 1 min; Detector, UV 254, 220 nm) to afford the title compound as an off-white solid (36 mg, 33% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$ (ppm): 11.35 (s, 1H), 8.50 (d, 1H), 7.52-7.57 (m, 2H), 7.39-7.40 (d, 1H), 6.94-6.98 (m, 2H), 4.69 (s, 2H), 4.19-4.22 (t, 2H), 3.78 (s, 3H), 3.64-3.68 (t, 2H). MS: (ES, m/z): 380 [M+H]<sup>+</sup>.

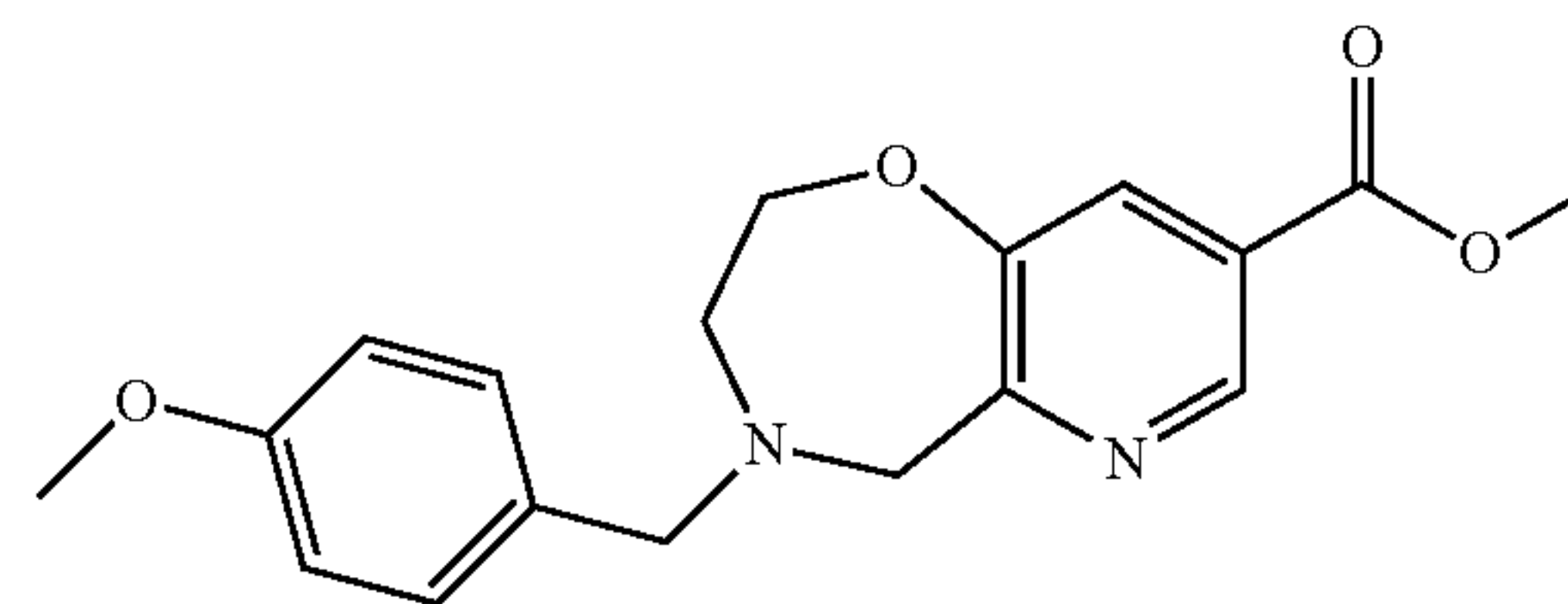
## Example 63

Preparation of N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxamide



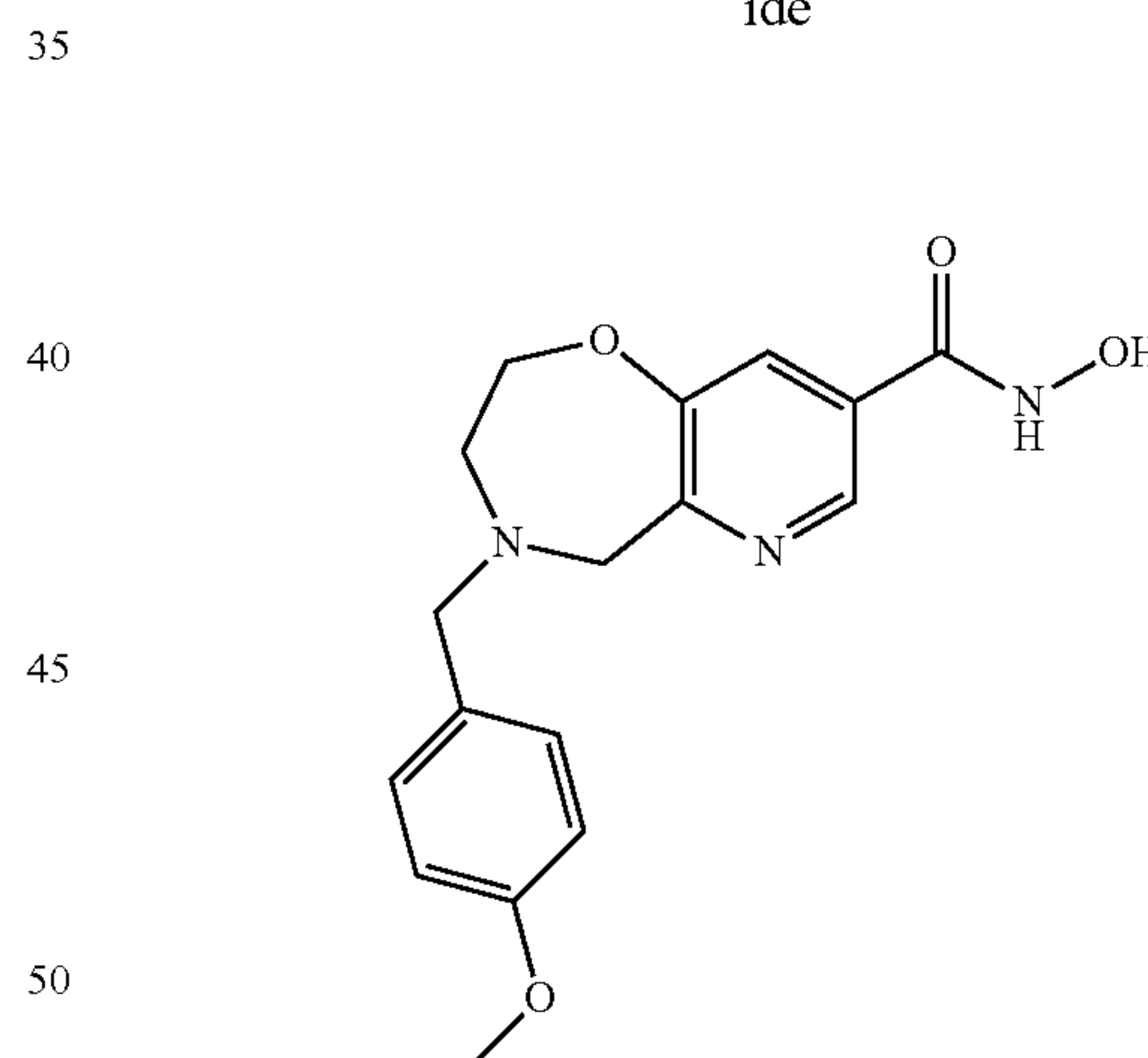
## 190

Step-1: Methyl 4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxylate



Into a 10-mL 2-necked round-bottom flask, was placed methyl 4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxylate (100 mg, 0.48 mmol, 1 equiv) and THF (4 mL) and then sodium hydride (23 mg, 0.96 mmol, 1.2 equiv) was added at 0° C. The resulting mixture was stirred for 0.5 h at 0° C. And then 1-(bromomethyl)-4-methoxybenzene (87 mg, 0.43 mmol, 0.9 equiv) was added. The resulting mixture was stirred for an additional 3 h at 25° C. The reaction was then quenched by the addition of NH<sub>4</sub>Cl. The resulting solution was extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 20:1) to afford the title compound as a yellow oil (100 mg, 63% yield). MS: (ES, m/z): 329 [M+H]<sup>+</sup>.

Step-2: N-Hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxamide



Into a 25-mL round-bottom flask, was placed methyl 4-[(4-methoxyphenyl)methyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxylate (100 mg, 0.31 mmol, 1 equiv), aq. 1N NaOH (0.61 mL, 2 equiv), NH<sub>2</sub>OH (0.6 g, 30 equiv, 50% in water) and MeOH/THF (4:1, 2 mL). The resulting solution was stirred for 1 h at 25° C. The pH value of the solution was adjusted to 6 with 3N HCl. The crude product was purified by Prep-HPLC (Column HSS C18 OBD, 1.8  $\mu$ m, 2.1×50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 23% B in 6 min, hold 1 min; Detector, UV 254, 220 nm) to afford the title compound as an orange solid (11 mg, 8% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$ (ppm): 11.49 (s, 1H), 9.35-10.56 (d, 1H), 8.63 (s, 1H), 7.77 (s, 1H),

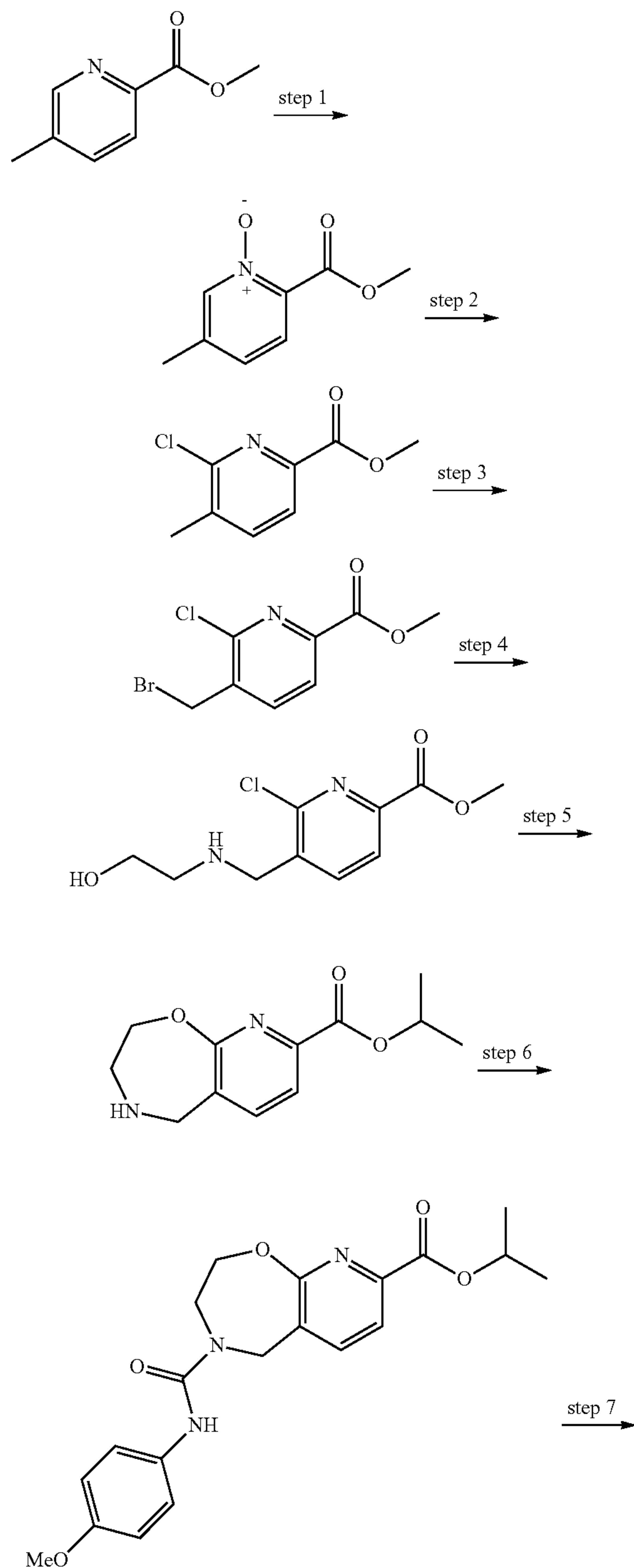


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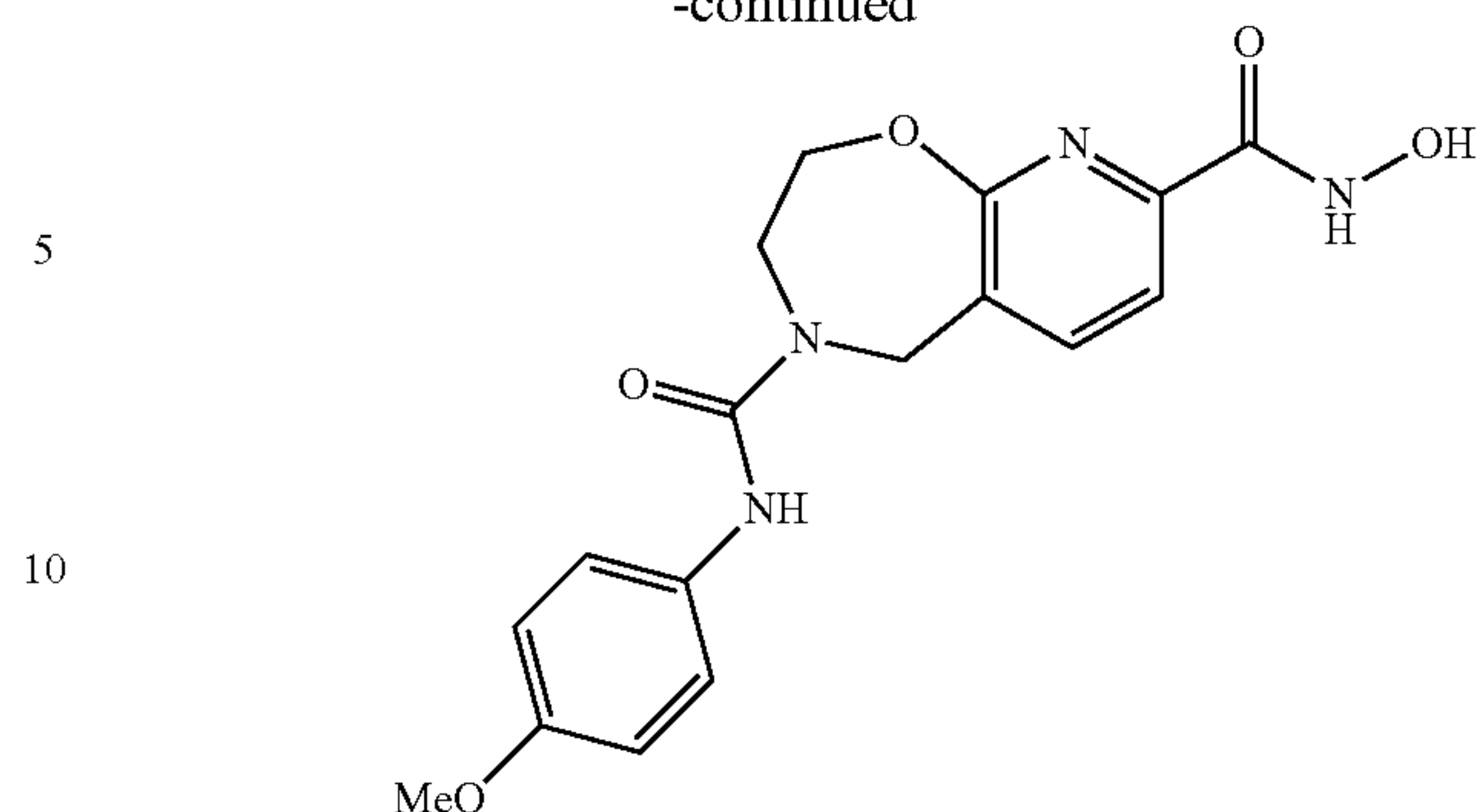
7.43-7.45 (d, 2H), 7.02-7.12 (t, 2H), 3.87-4.52 (m, 8H), 3.76-3.79 (d, 3H). MS: (ES, m/z): 330 [M+H]<sup>+</sup>.

**Example 64**

Preparation of N8-hydroxy-N4-(4-methoxyphenyl)-2,3-dihydropyrido[3,2-f][1,4]oxazepine-4,8(5H)-dicarboxamide

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-continued



Step-1: 2-(Methoxycarbonyl)-5-methylpyridine 1-oxide

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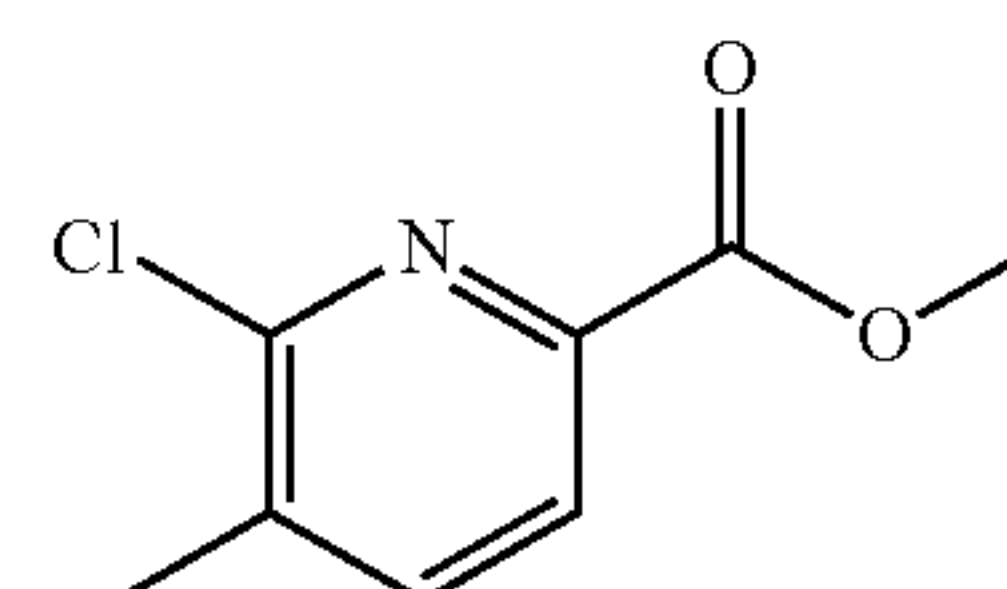
55

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Into a 3 L 3-necked round-bottom flask, was placed methyl 5-methylpicolinate (43.7 g, 289 mmol, 1 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1 L). This was followed by the addition of 3-chlorobenzene-1-carboxoperoxoic acid (106 g, 614 mmol, 2 equiv) in several batches at 0° C. The resulting mixture was stirred overnight at room temperature. The reaction was then quenched with sat. aq. Na<sub>2</sub>SO<sub>3</sub> (500 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×100 mL). The combined organic layers were washed with sat. aq. NaHCO<sub>3</sub> solution (400 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The crude product was re-crystallized from pet. ether:CH<sub>2</sub>Cl<sub>2</sub> (20:1) to afford the title compound as a yellow solid (40 g, 83% yield). MS: (ES, m/z): 168 [M+H]<sup>+</sup>.

Step-2: Methyl 6-chloro-5-methylpyridine-2-carboxylate

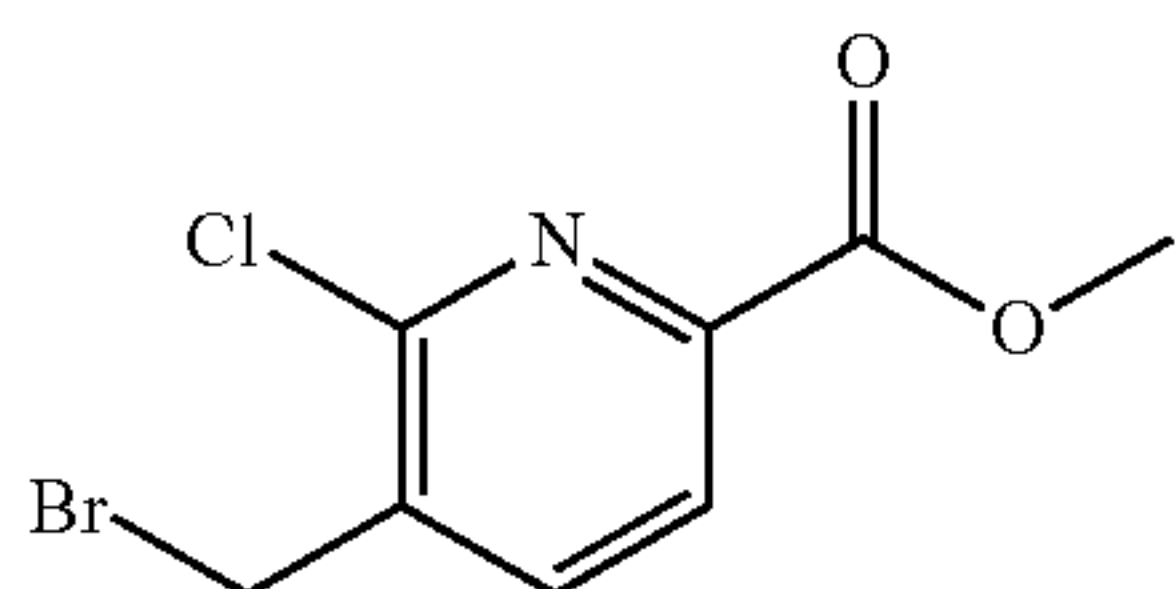


Into a 100-mL round-bottom flask, was placed 2-(methoxycarbonyl)-5-methylpyridine 1-oxide (10 g, 59.82 mmol, 1 equiv) and chloroform (50 mL), followed by the addition of phosphoroyl trichloride (42.2 mL, 9 equiv) dropwise with stirring. The resulting solution was stirred overnight at 80° C. in an oil bath. The resulting mixture was concentrated under vacuum and then quenched with water (20 mL). The pH value of the solution was adjusted to 7 with K<sub>2</sub>CO<sub>3</sub> (10% in water) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with H<sub>2</sub>O (3×20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by

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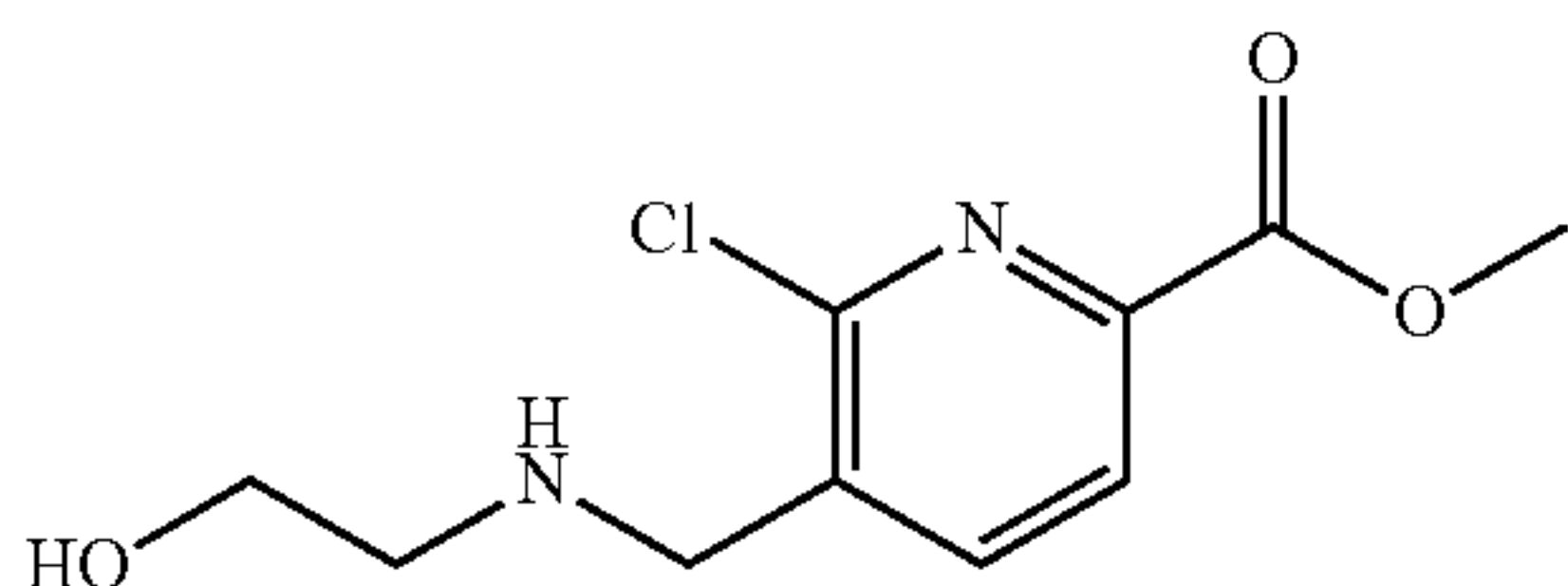
silica gel chromatography (Gradient 0-10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a yellow solid (7 g, 57% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 7.96-8.02 (m, 2H), 3.88 (s, 1H), 2.41-2.51 (m, 3H). MS: (ES, m/z): 186 [M+H]<sup>+</sup>.

Step-3: Methyl  
5-(bromomethyl)-6-chloropyridine-2-carboxylate



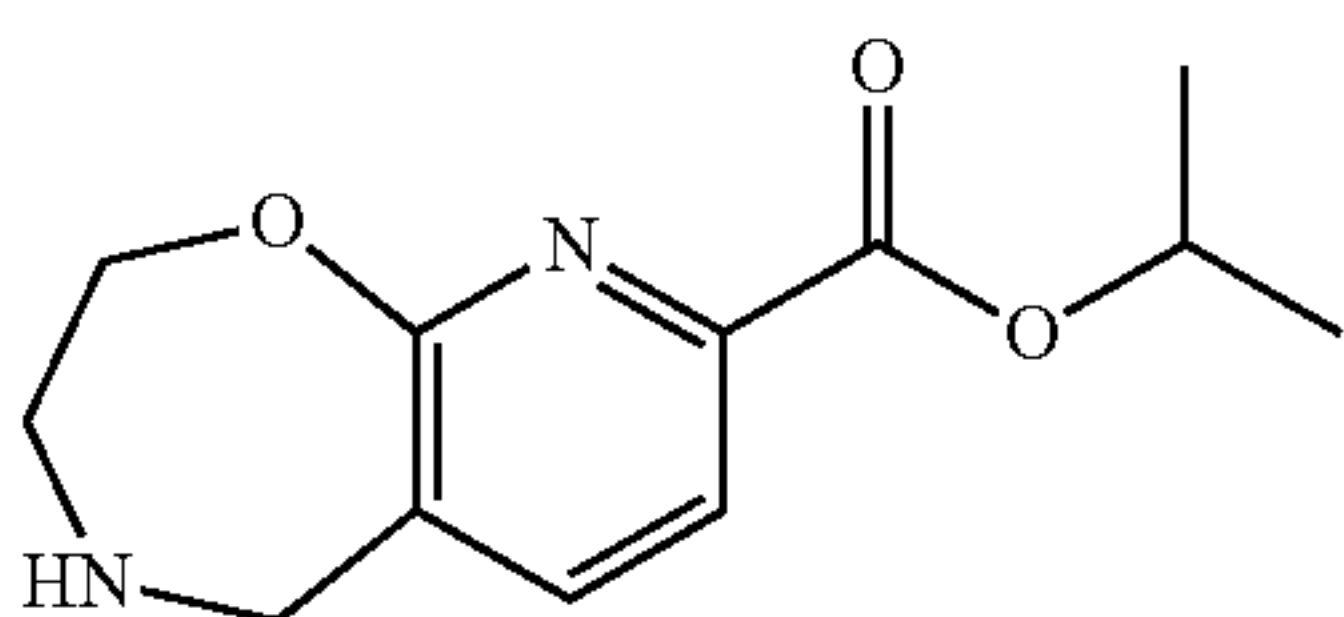
Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed methyl 6-chloro-5-methylpyridine-2-carboxylate (4.2 g, 22.63 mmol, 1 equiv), benzoyl peroxide (549.9 mg, 2.27 mmol, 0.1 equiv), NBS (4.04 g, 22.70 mmol, 1 equiv) and CCl<sub>4</sub> (35 mL). The resulting mixture was stirred overnight at 80° C. in an oil bath. The reaction was concentrated under vacuum and quenched with water (20 mL), then extracted with EtOAc (3×30 mL). The combined organic layers were washed with H<sub>2</sub>O (3×20 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (Gradient 0-10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a yellow solid (2.5 g, 38% yield). MS: (ES, m/z): 265 [M+H]<sup>+</sup>.

Step-4: Methyl 6-chloro-5-(((2-hydroxyethyl)amino)methyl)picolinate



Into a 50-mL round-bottom flask, was placed a solution of 2-aminoethan-1-ol (1.4 g, 22.89 mmol, 2 equiv) in MeCN (20 mL) and K<sub>2</sub>CO<sub>3</sub> (4.74 g, 34.03 mmol, 3 equiv). This was followed by the addition of a solution of methyl 5-(bromomethyl)-6-chloropyridine-2-carboxylate (3 g, 11.34 mmol, 1 equiv) in MeCN (10 mL) dropwise with stirring. The resulting mixture was stirred for 1 h at room temperature. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography (Gradient 0-10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a yellow solid (1.5 g, 49% yield). MS: (ES, m/z): 245 [M+H]<sup>+</sup>.

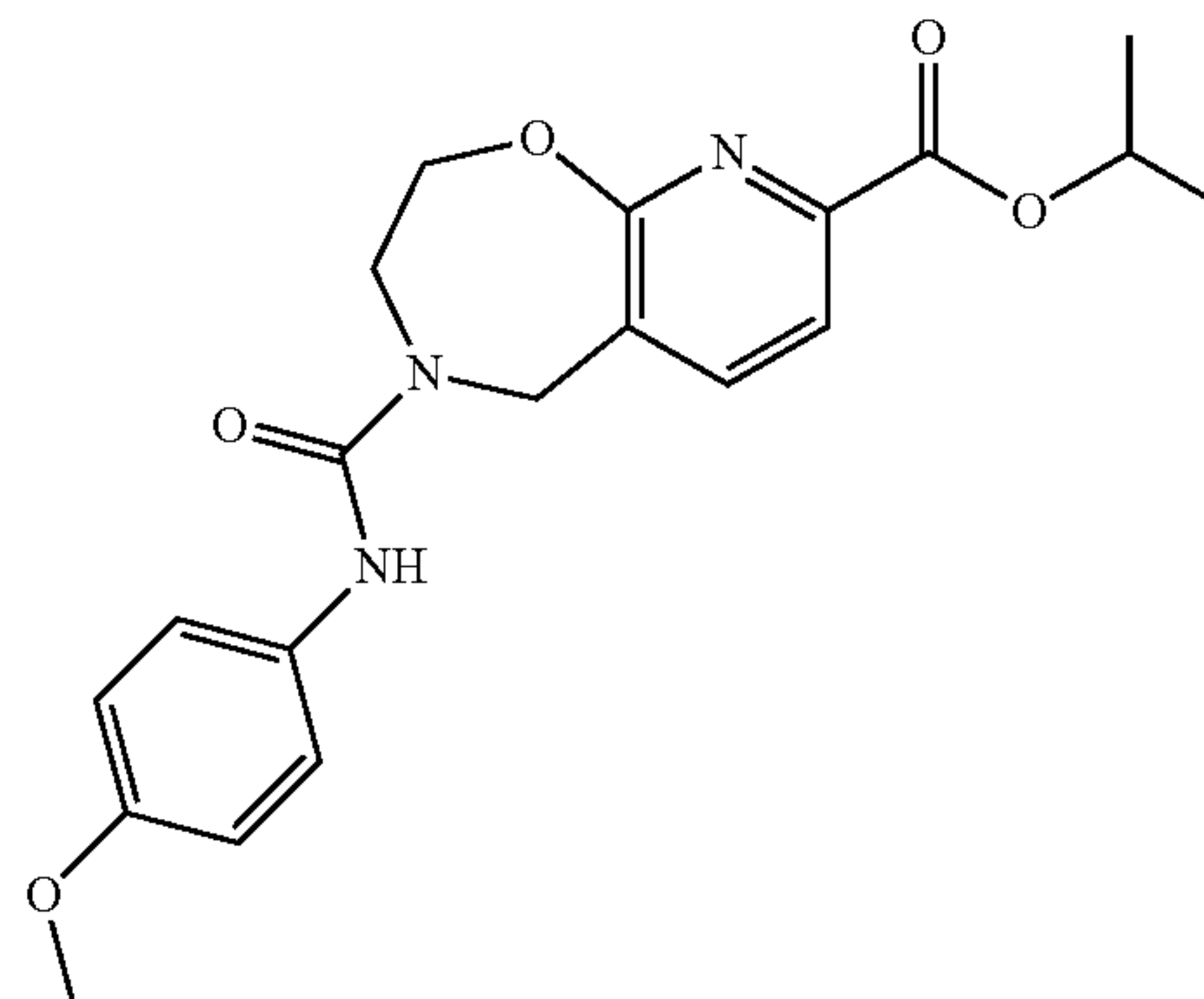
Step-5: Isopropyl 2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxylate



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Into 20-mL sealed tube, was placed methyl 6-chloro-5-(((2-hydroxyethyl)amino)methyl)picolinate (1 g, 4.09 mmol, 1 equiv), K<sub>2</sub>CO<sub>3</sub> (1.103 g, 7.98 mmol, 2 equiv), isopropanol (10 mL) and CuI (156 mg, 0.82 mmol, 0.2 equiv). The resulting solution was stirred overnight at 110° C. in an oil bath. The reaction was then quenched with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with H<sub>2</sub>O (3×10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue purified by silica gel chromatography (Gradient 0-10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a green solid (148 mg, 14% yield). MS: (ES, m/z): 237 [M+H]<sup>+</sup>.

Step-6: Isopropyl 4-(((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxylate

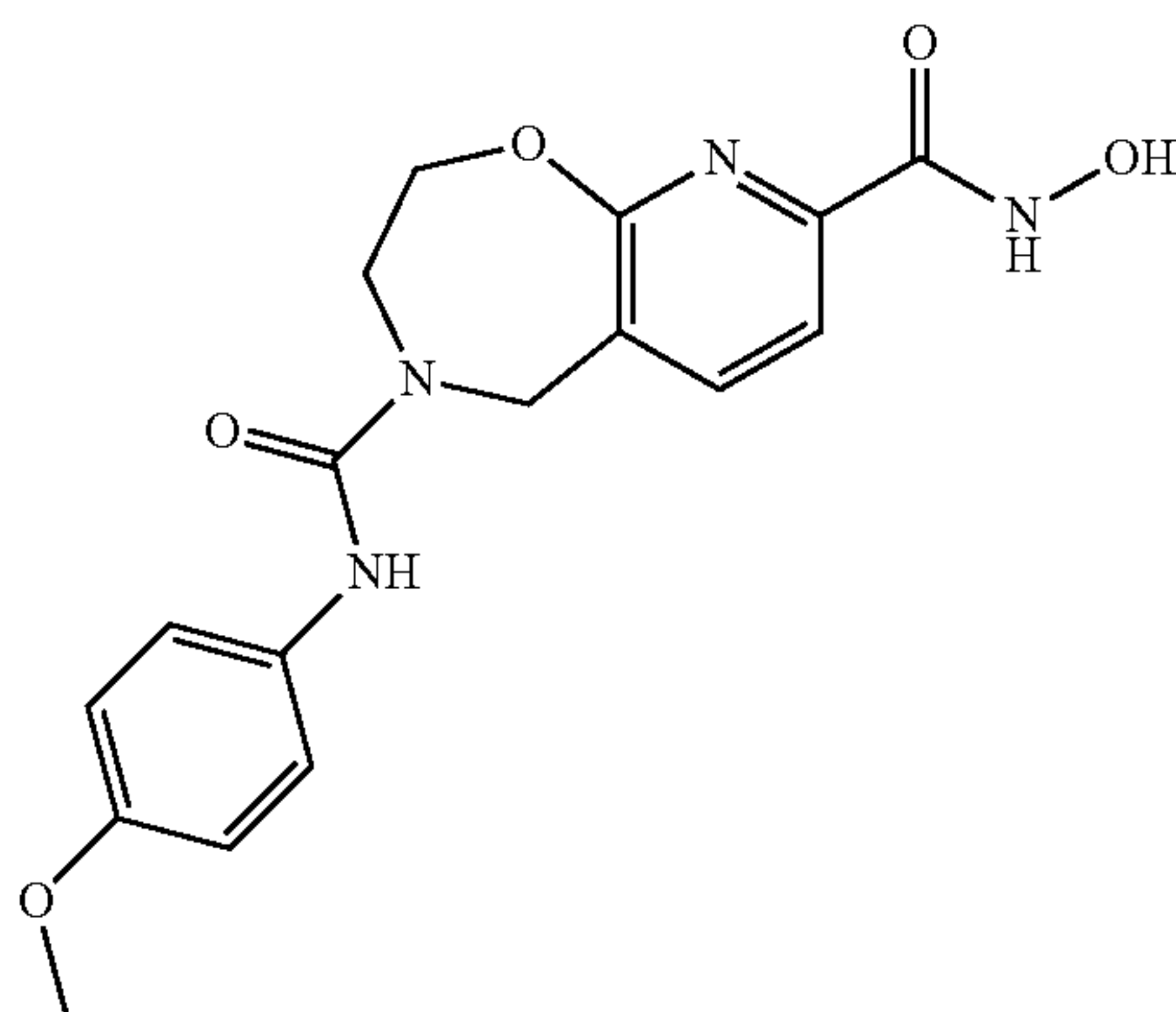


Into a 8-mL vial, was placed a solution of isopropyl 2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxylate (30 mg, 0.13 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) and Et<sub>3</sub>N (14 mg, 0.14 mmol, 1.1 equiv). The resulting mixture was stirred for 30 min at 0° C. This was followed by the addition of a solution of 1-isocyanato-4-methoxybenzene (21 mg, 0.14 mmol, 1.1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) dropwise with stirring at 0° C. The mixture was stirred for 4 h at room temperature and then concentrated. The residue purified by silica gel chromatography (Gradient 0-40% EtOAc/pet. ether) to afford the title compound as a yellow oil (42 mg, 86% yield). MS: (ES, m/z): 386 [M+H]<sup>+</sup>.



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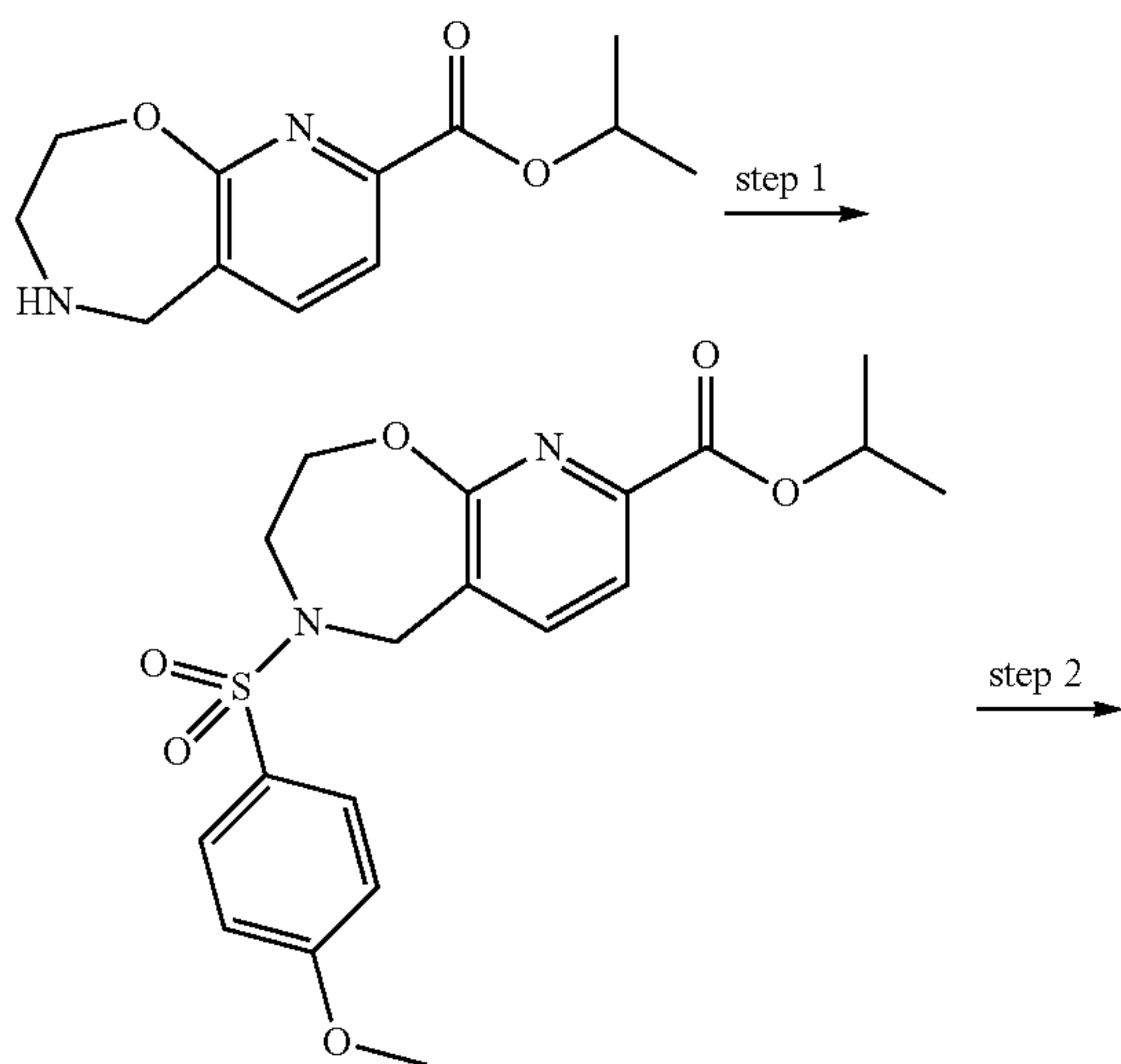
Step-7: N8-Hydroxy-N4-(4-methoxyphenyl)-2,3-dihydropyrido[3,2-f][1,4]oxazepine-4,8(5H)-dicarboxamide



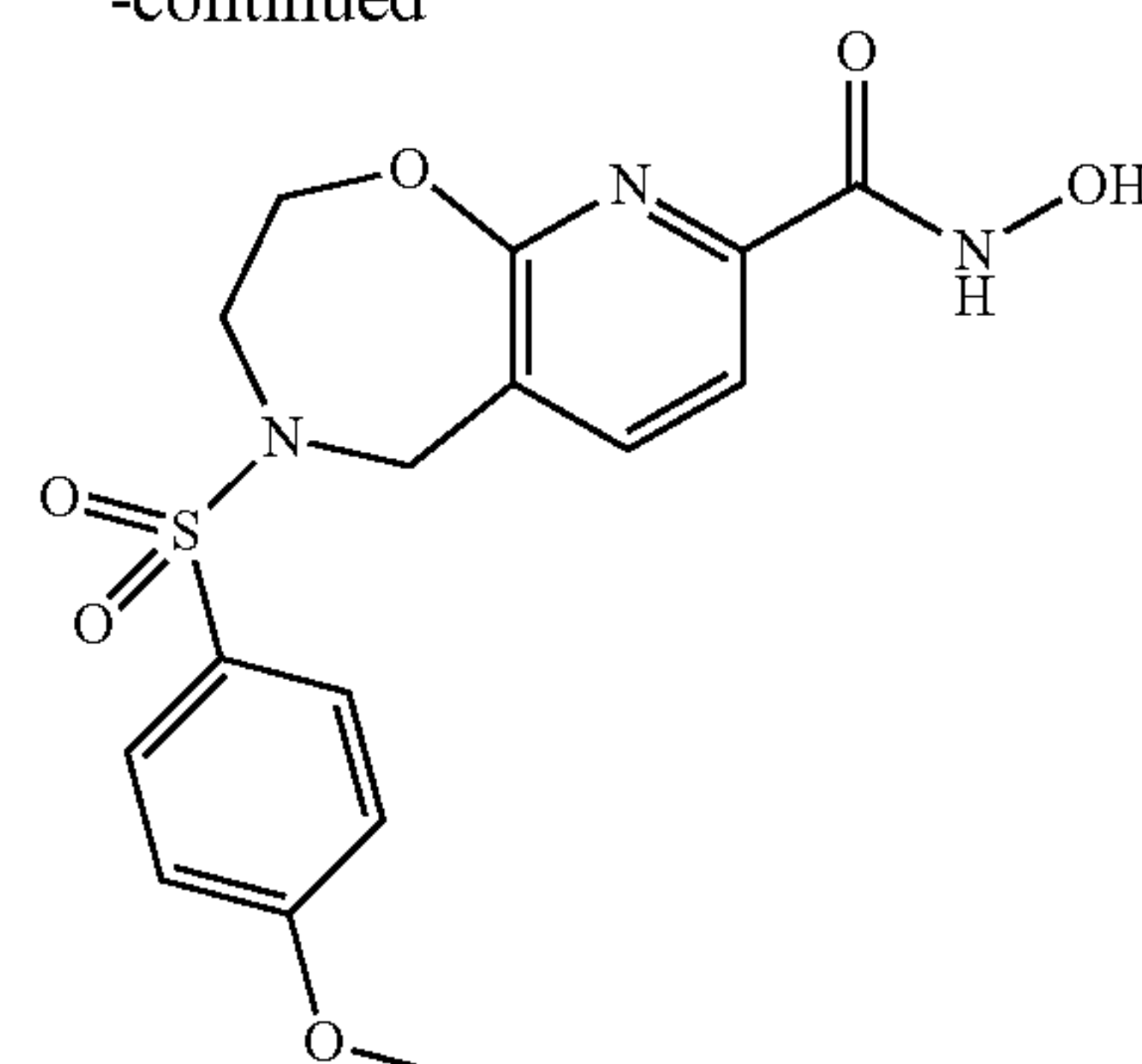
Into a 8-mL vial, was placed isopropyl 4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxylate (42 mg, 0.11 mmol, 1 equiv),  $\text{NH}_2\text{OH}$  (0.864 g, 120 equiv, 50% in water), aq. 1N NaOH (0.218 mL, 2 equiv), THF/MeOH (2 mL, 4:1). The resulting mixture was stirred for 1 h at room temperature, then cooled to 0° C. and the pH value of the solution was adjusted to 6 with 6N HCl. The crude product was purified by Prep-HPLC (Column: HSS C18 OBD, 1.8  $\mu\text{m}$ , 2.1x50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2 min, hold 0.6 min; Detector, UV 254, 220 nm) to afford the title compound as a pink solid (17 mg, 32% yield).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.23 (s, 1H), 9.01 (s, 1H), 8.42 (s, 1H), 7.92-7.94 (d, J=8 Hz, 1H), 7.64-7.66 (d, J=8 Hz, 1H), 7.26-7.28 (d, J=8 Hz, 1H), 6.78-6.80 (d, J=8 Hz, 1H), 4.71 (s, 1H), 4.33-4.35 (t, J=4 Hz, 2H), 3.89-3.90 (t, J=4 Hz, 2H), 3.34 (s, 3H). MS: (ES, m/z): 359  $[\text{M}+\text{H}]^+$ .

**Example 65**

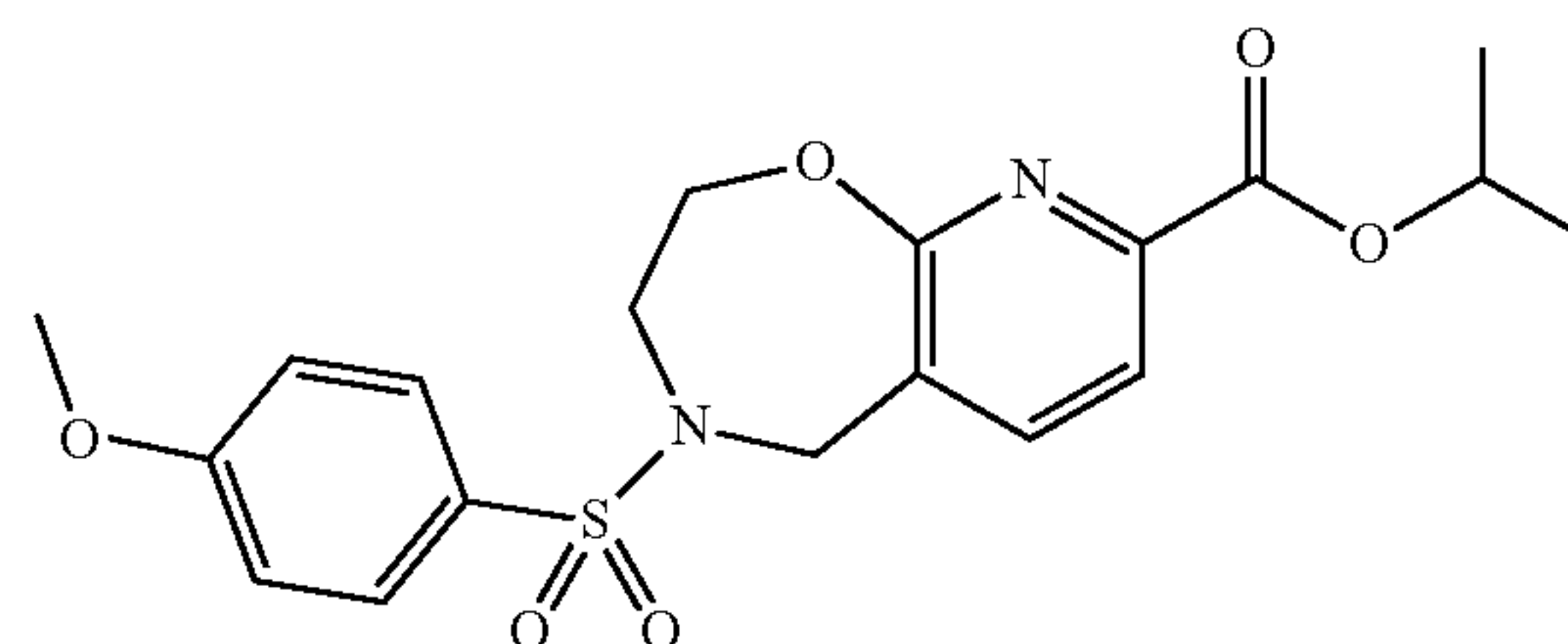
Preparation of N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxamide

**196**

-continued

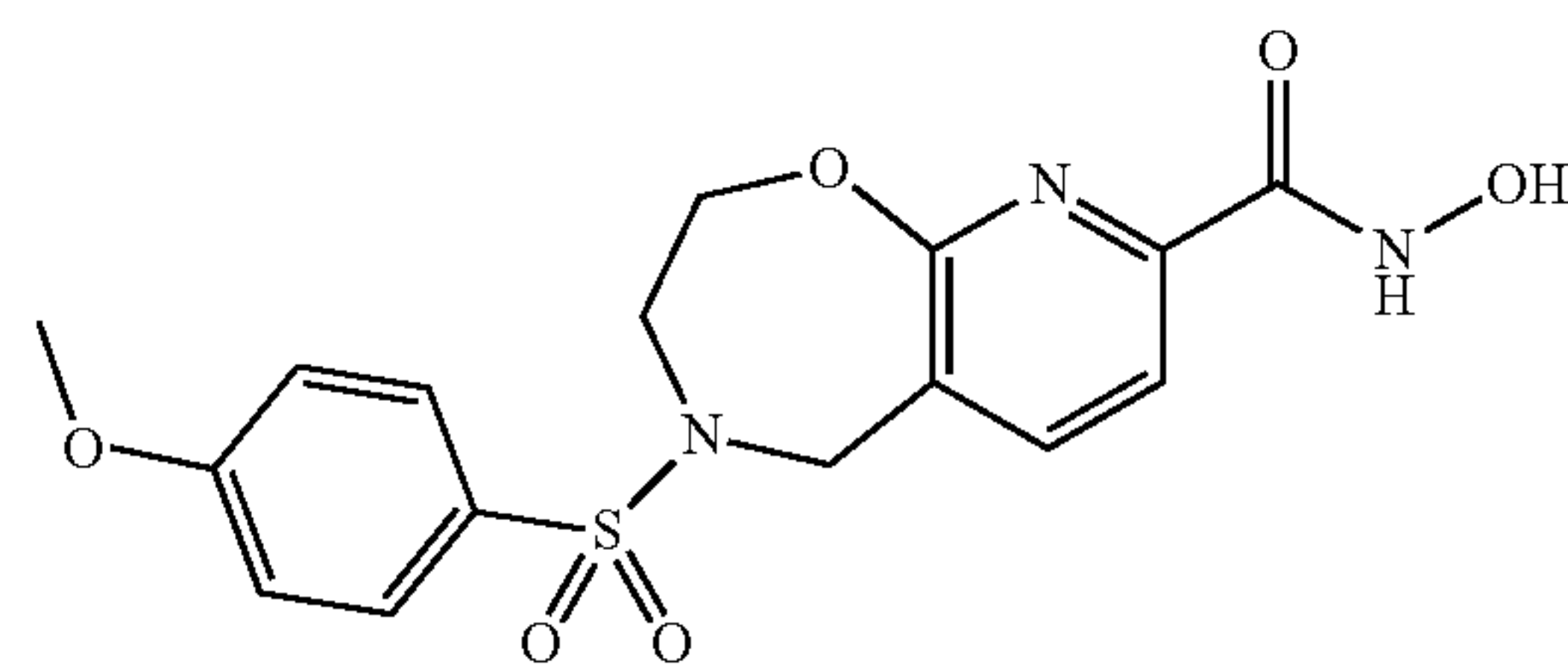


Step-1: Isopropyl 4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed isopropyl 2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxylate (30 mg, 0.13 mmol, 1 equiv),  $\text{CH}_2\text{Cl}_2$  (2.5 mL) and  $\text{Et}_3\text{N}$  (14 mg, 0.14 mmol, 1.10 equiv). The resulting mixture was stirred for 30 min at 0° C. This was followed by the addition of 4-methoxybenzene-1-sulfonyl chloride (26.18 g, 112 mmol, 1 equiv) dropwise with stirring at 0° C. The mixture was allowed to react, with stirring, for additional 2 h at room temperature and concentrated. The residue purified by silica gel chromatography (Gradient 0-5% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to afford the title compound as a brown solid (57 mg) which was used without further purification. MS: (ES, m/z): 407  $[\text{M}+\text{H}]^+$ .

Step-2: N-Hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxamide



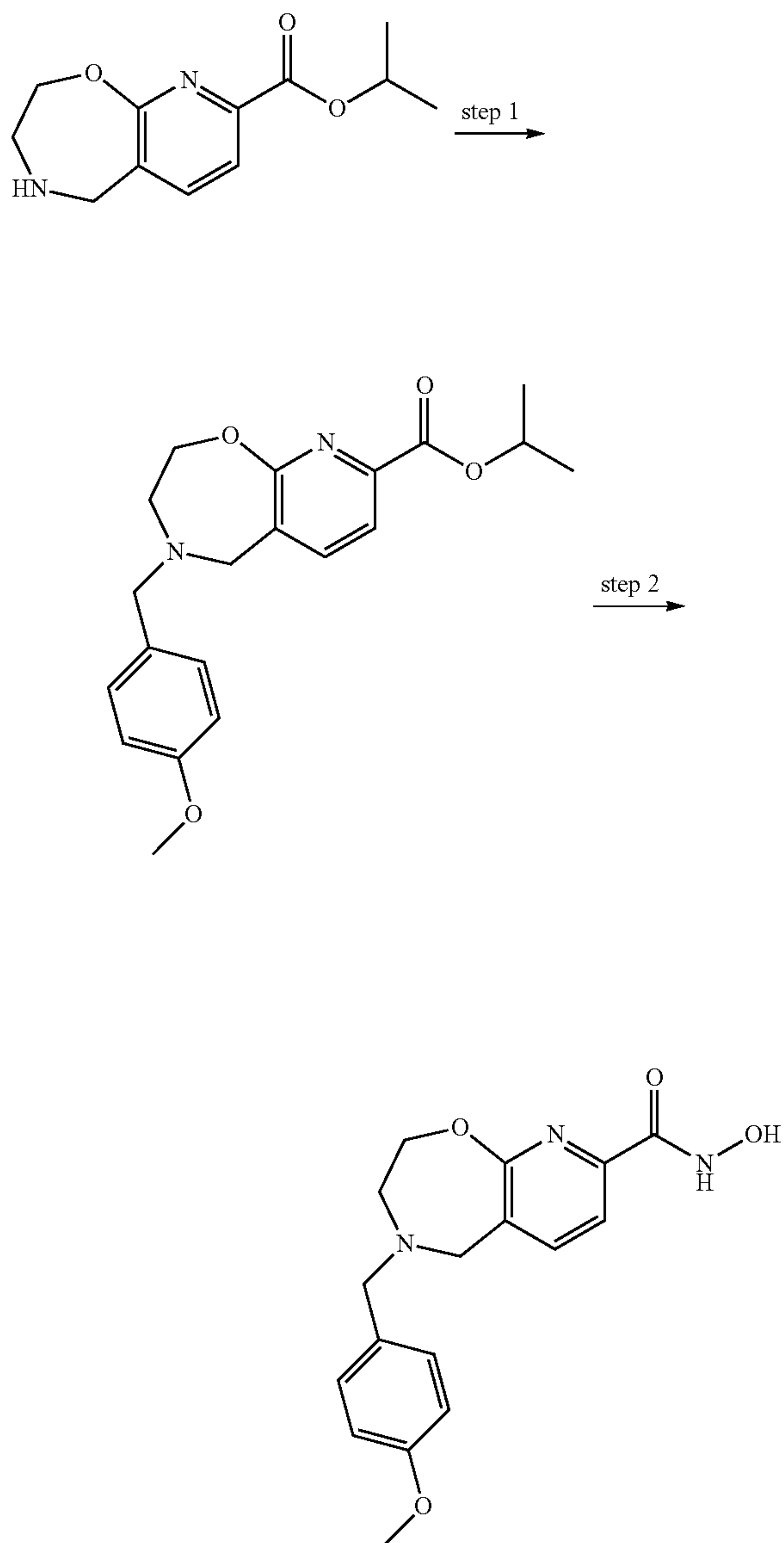
Into a 8-mL vial, was placed a solution of isopropyl 4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxylate (57 mg, 0.14 mmol, 1 equiv) in THF/MeOH (2 mL, 4:1),  $\text{NH}_2\text{OH}$  (1.11 g, 16.82 mmol, 120 equiv, 50% in water), and aq. 1N NaOH (0.28 mL, 2 equiv). The mixture was stirred for 1 h at room

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temperature. The pH value of the solution was adjusted to 6 with 6N HCl. The crude product was purified by Prep-HPLC (Column: HSS C18 OBD, 1.8  $\mu$ m, 2.1 $\times$ 50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2 min, hold 0.6 min; Detector, UV 254, 220 nm) to afford the title compound as a pink solid (13 mg, 19% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ (ppm): 11.19 (s, 1H), 9.01 (s, 1H), 7.87-7.89 (d, J=8 Hz, 1H), 7.60-7.64 (m, 3H), 6.99-7.01 (d, J=8 Hz, 2H), 4.54 (s, 2H), 4.26-4.28 (t, J=4 Hz, 2H), 3.76 (s, 3H), 3.62-3.63 (t, J=8 Hz, 2H). MS: (ES, *m/z*): 380 [M+H]<sup>+</sup>.

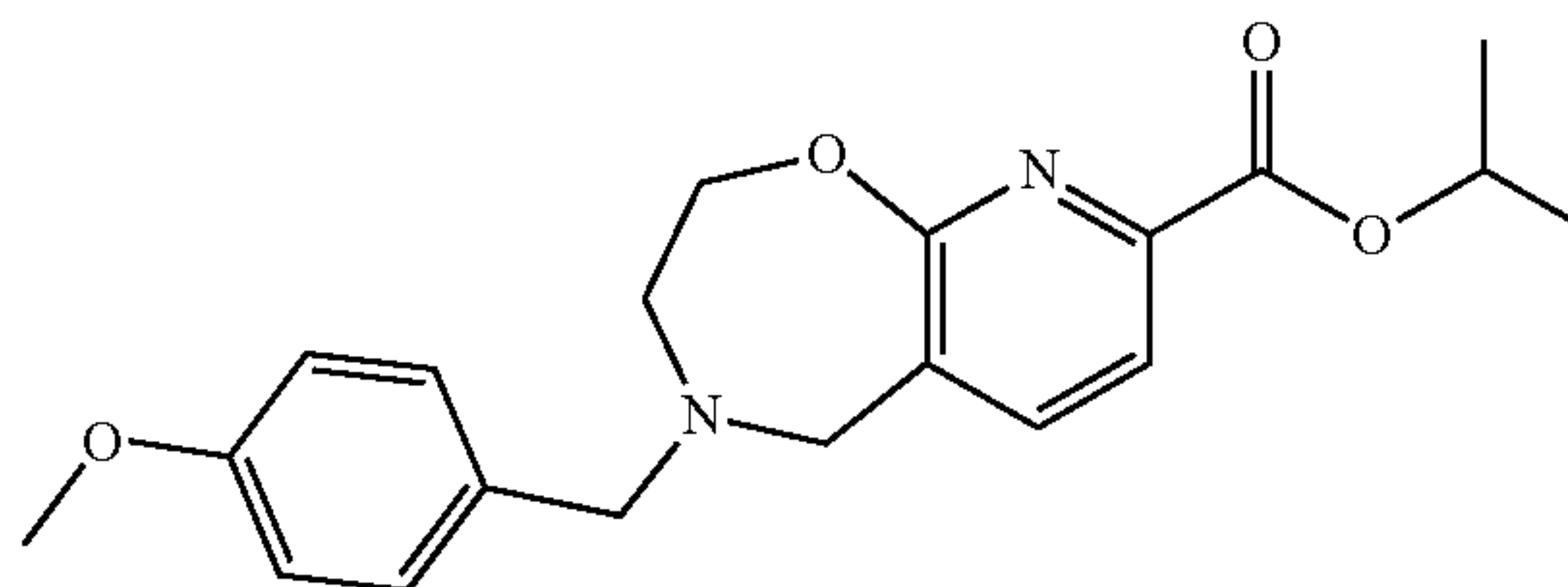
## Example 66

Preparation of N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxamide



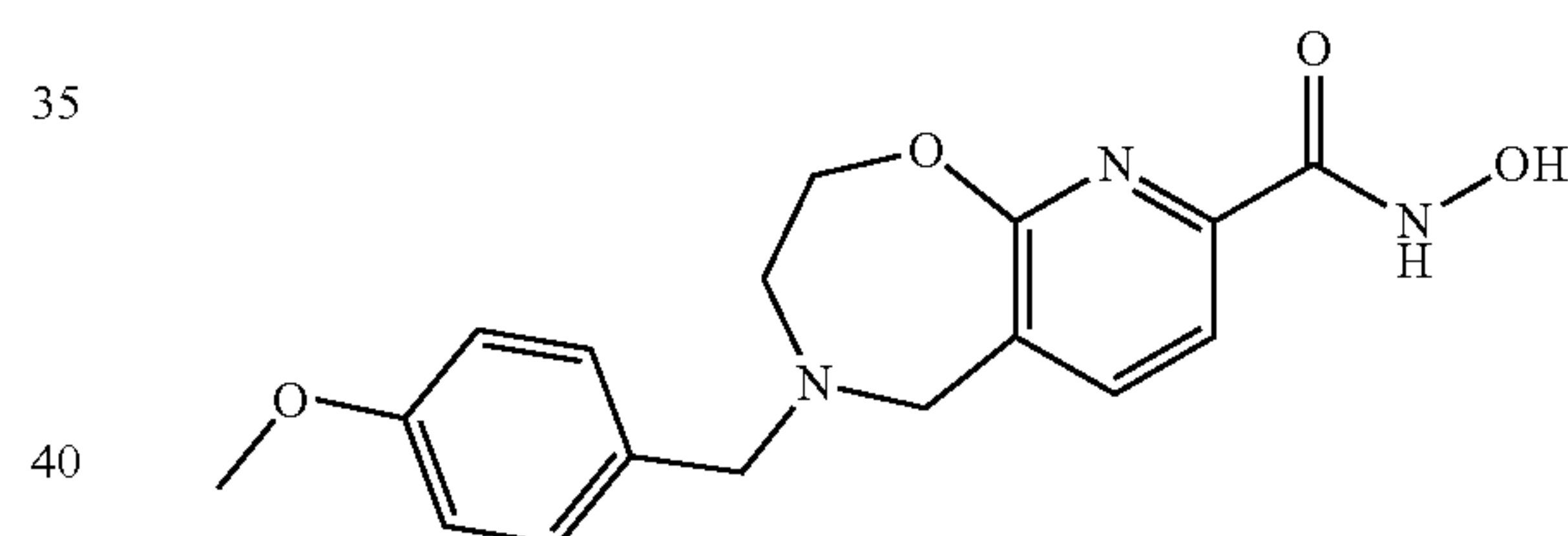
## 198

Step-1: Isopropyl 4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxylate



Into a 8-mL vial, was placed isopropyl 2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxylate (50 mg, 0.21 mmol, 1 equiv), 4-methoxybenzaldehyde (30.25 mg, 0.22 mmol, 1.05 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL). The resulting mixture was stirred for 30 min at room temperature. Then NaBH(OAc)<sub>3</sub> (449 mg, 2.12 mmol, 10 equiv) was added. The mixture was stirred overnight at room temperature and concentrated. The residue purified by silica gel chromatography (Gradient 0-40% EtOAc.pet. ether) to afford the title compound as a yellow oil (59 mg, 78% yield). MS: (ES, *m/z*): 357 [M+H]<sup>+</sup>.

Step-2: N-Hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxamide



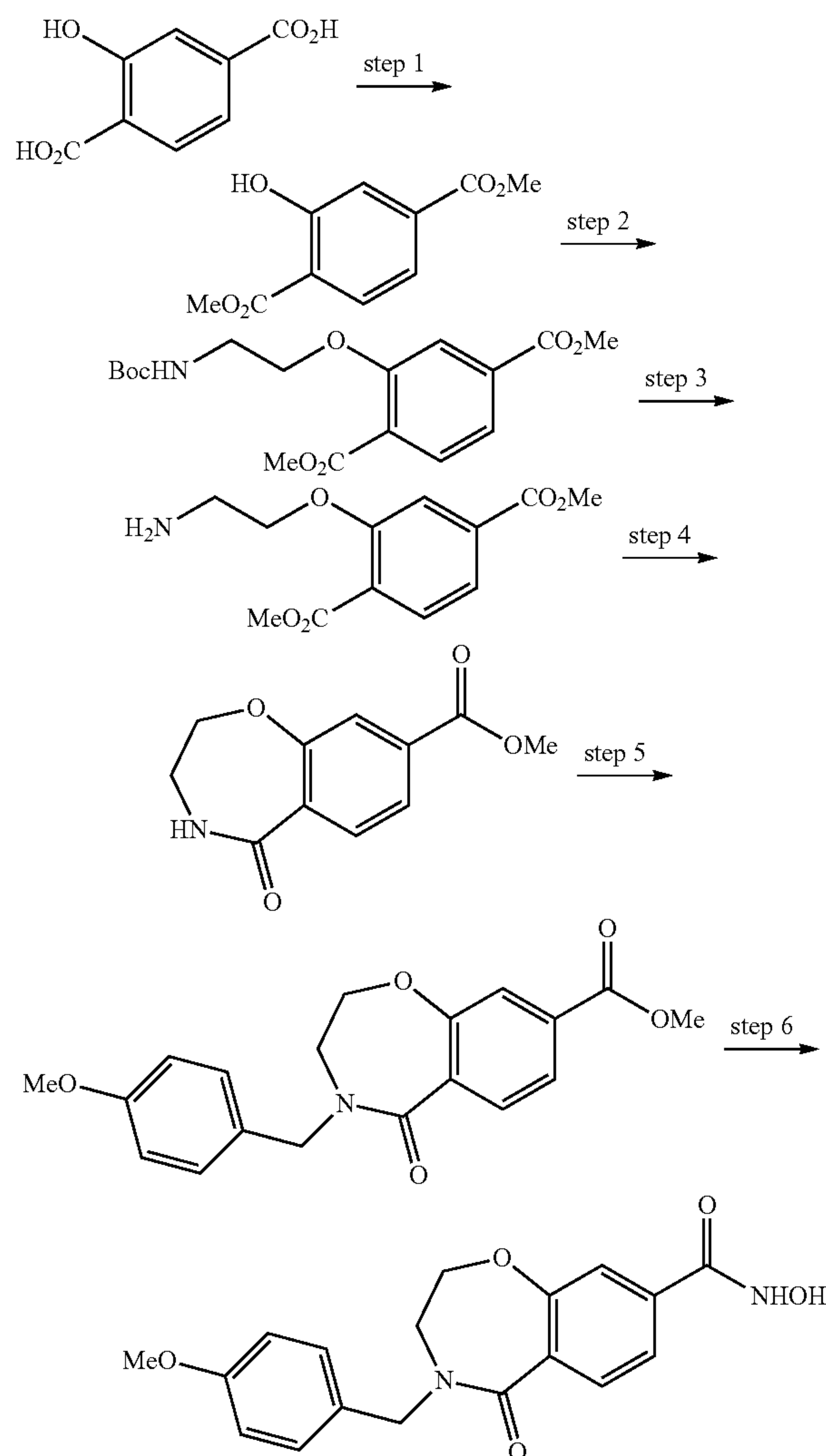
Into a 8-mL vial, was placed isopropyl 4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxylate (63 mg, 0.18 mmol, 1 equiv), NH<sub>2</sub>OH (1.4 g, 120 equiv, 50% in water), aq. 1N NaOH (0.35 mL, 2 equiv) and THF/MeOH (2 mL, 4:1). The resulting mixture was stirred for 1 h at room temperature. The pH value of the solution was adjusted to 6 with 6N HCl. The crude product was purified by Prep-HPLC (Column: HSS C18 OBD, 1.8  $\mu$ m, 2.1 $\times$ 50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2 min, hold 0.6 min; Detector, UV 254, 220 nm) to afford the title compound as a pink solid (33 mg, 42% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ (ppm): 11.39 (s, 1H), 10.60 (br s, 1H), 9.11 (br s, 1H), 7.94 (s, 1H), 7.76-7.78 (d, J=8 Hz, 1H), 7.42 (s, 2H), 7.01-7.03 (d, J=8 Hz, 2H), 4.28-4.69 (m, 7H), 3.71-3.86 (m, 4H). MS: (ES, *m/z*): 330 [M+H]<sup>+</sup>.



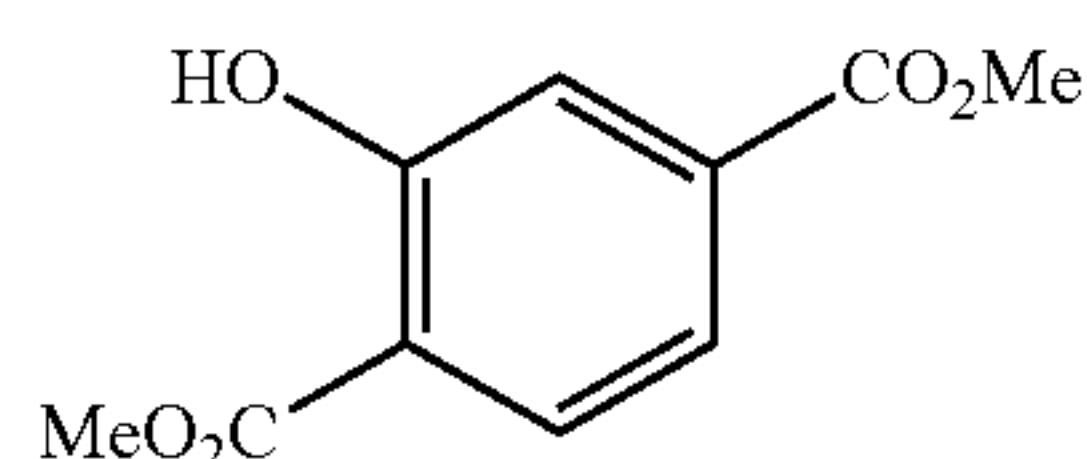
## 199

## Example 67

## Preparation of N-Hydroxy-4-(4-methoxybenzyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



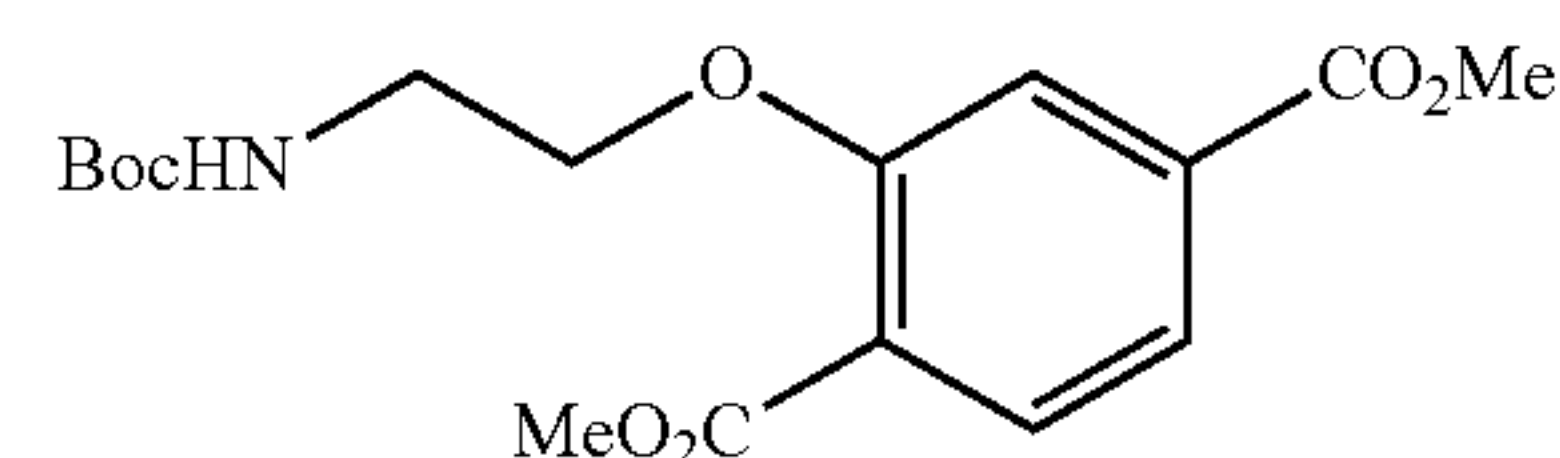
## Step-1: Dimethyl 2-hydroxyterephthalate



2-Hydroxyterephthalic acid (5 g, 27.5 mmol) was refluxed in MeOH (120 mL), containing 0.15 mL of conc.  $\text{H}_2\text{SO}_4$ . After 22 h the reaction mixture was concentrated under reduced pressure and the residue was redissolved in  $\text{CH}_2\text{Cl}_2$  and washed sequentially with water, saturated aqueous solution of  $\text{NaHCO}_3$ , brine and dried over  $\text{Na}_2\text{SO}_4$ . The solution was filtered and concentrated. The crude material was purified by silica gel chromatography (Gradient: EtOAc/hexanes) to afford the title compound (1.7 g, 31% yield).

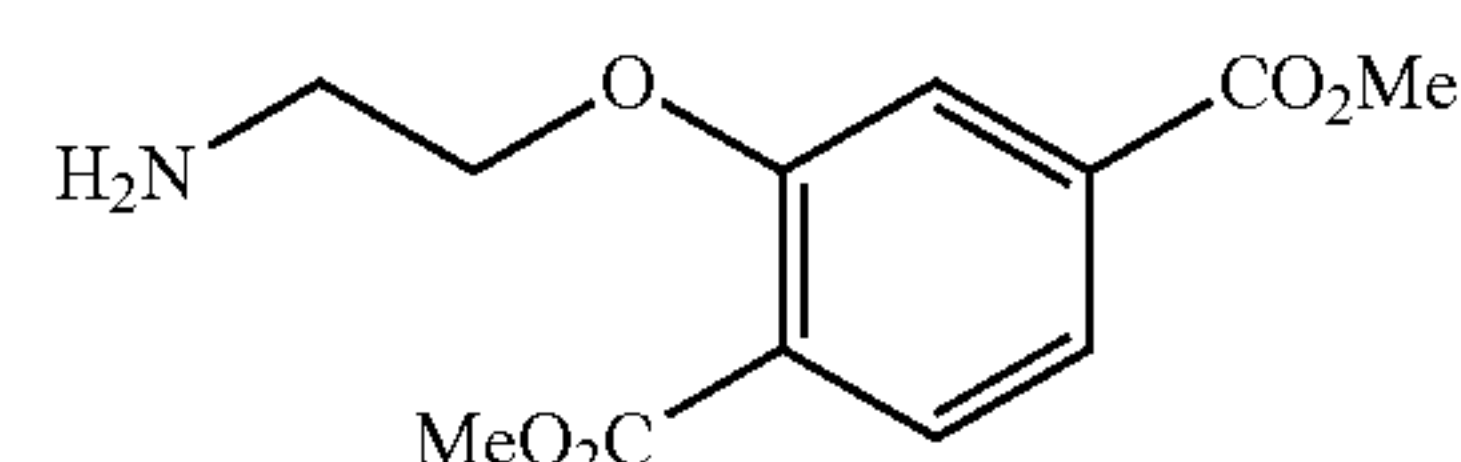
## 200

## Step-2: Dimethyl 2-((tert-butoxycarbonyl)amino)ethoxyterephthalate



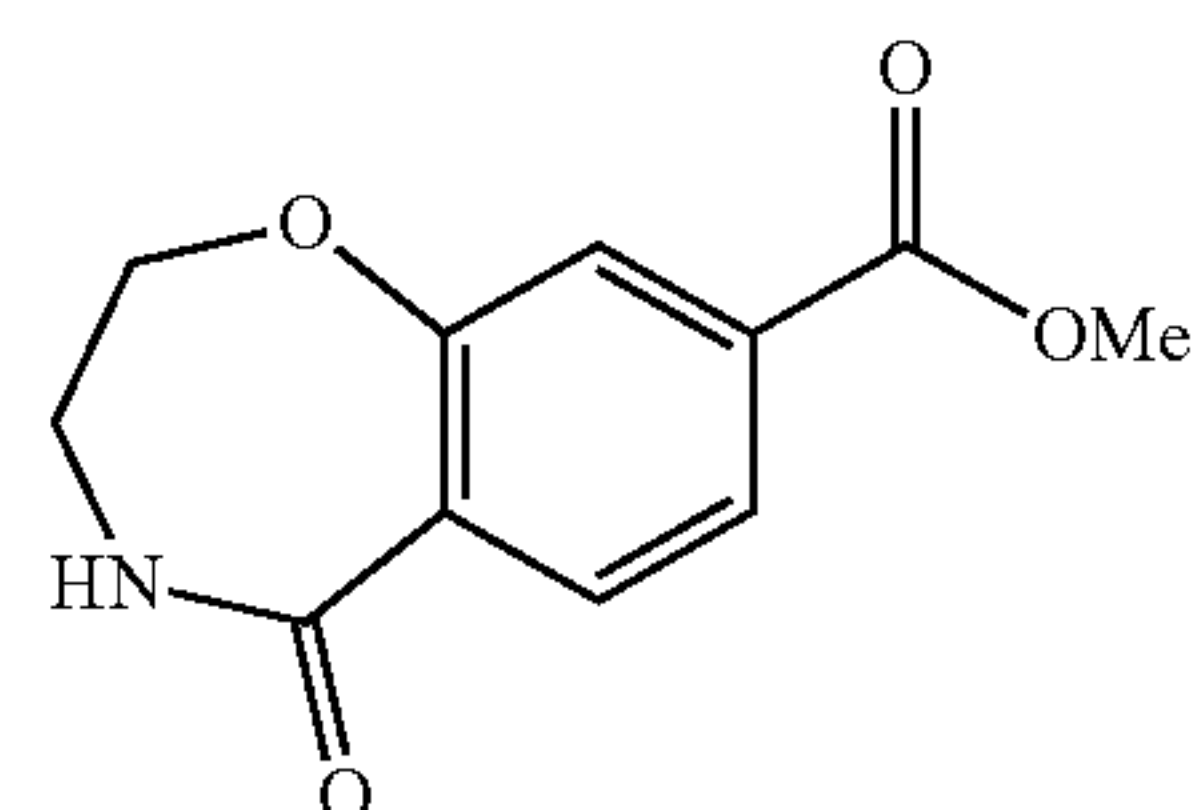
To a suspension of dimethyl 2-hydroxyterephthalate (0.7 g, 3.3 mmol, 1 equiv) in THF (8 mL), tert-butyl (2-hydroxyethyl)carbamate (0.62 mL, 4.0 mmol, 1.2 equiv) and triphenylphosphine (1.4 g, 5.3 mmol, 1.6 equiv) were added at room temperature. The mixture was cooled to 0° C. and DEAD (0.84 mL, 5.3 mmol, 1.6 equiv) was added and the resulting mixture was slowly warmed up to room temperature and stirred 72 h. The mixture was concentrated and purified by silica gel chromatography (Gradient: EtOAc/hexanes) to afford the title compound (1.15 g, quantitative yield).

## Step-3: Dimethyl 2-(2-aminoethoxy)terephthalate



Dimethyl 2-((tert-butoxycarbonyl)amino)ethoxyterephthalate (1.18 g, 3.34 mmol) was mixed with  $\text{CH}_2\text{Cl}_2$  (3 mL) and then TFA (1.5 mL) was added at room temperature. The reaction mixture was stirred overnight at room temperature, then concentrated and co-evaporated several times with toluene. After trituration in MeOH/Et<sub>2</sub>O the title compound was obtained as its TFA salt (1.15 g, quantitative yield).

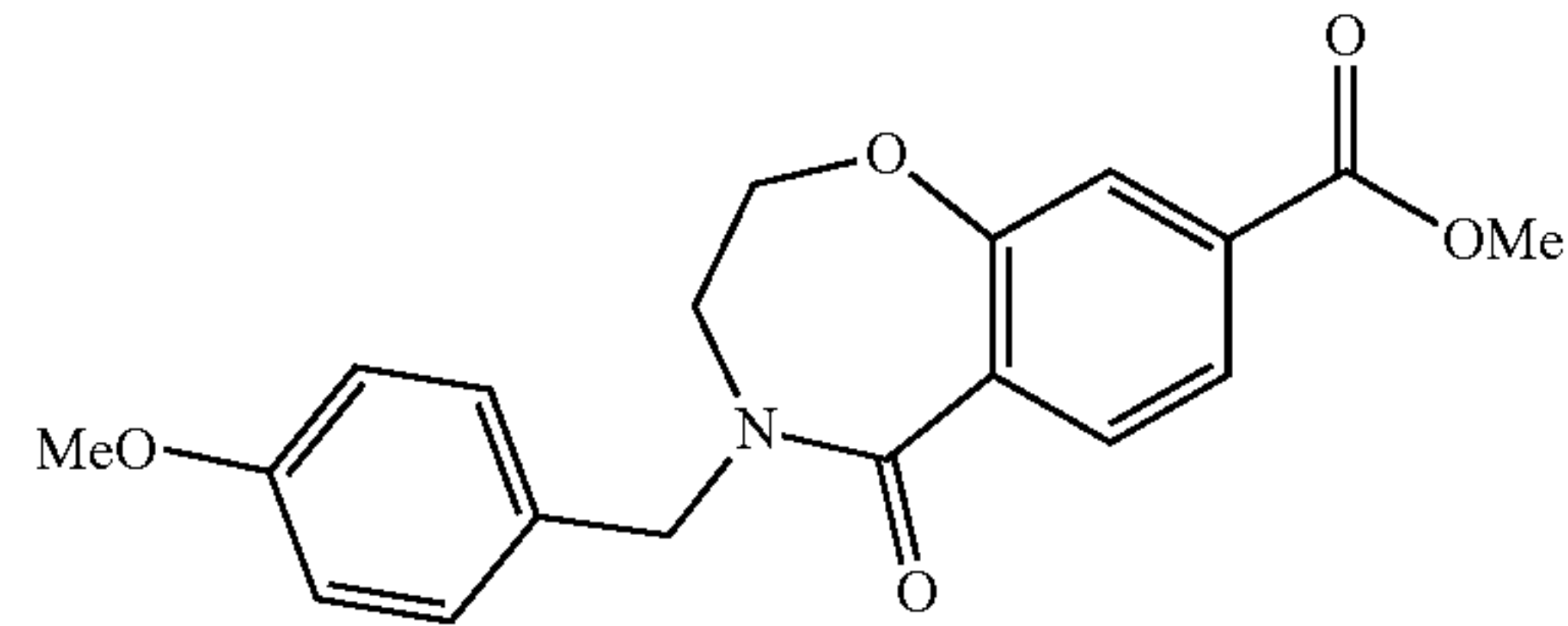
## Step-4: Methyl 5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



Dimethyl 2-(2-aminoethoxy)terephthalate (1.15 g, 3.3 mmol) was mixed with toluene (7 mL) and Et<sub>3</sub>N (1.9 mL, 13.3 mmol) and stirred at 105° C. After 20 h, the reaction mixture was cooled to room temperature, concentrated and purified by silica gel chromatography (Gradient EtOAc/hexanes) to afford the title compound (380 mg, 52% yield). m. p.=149-150° C. <sup>1</sup>H-NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 8.0.2 (d, J=8.25 Hz, 1H), 7.87, (d, J=8.25 Hz, 1H), 7.76 (dd, J=8.25, 1.65 Hz, 1H), 7.25 (d, J=8.25 Hz, 1H), 6.73 (br. s, 1H), 4.44-4 (m, 2H), 3.93 (s, 3H), 3.54-3.50 (m, 2H). MS: (APCI, m/z): 222 [M+H]<sup>+</sup>.

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Step-5: Methyl 4-(4-methoxybenzyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

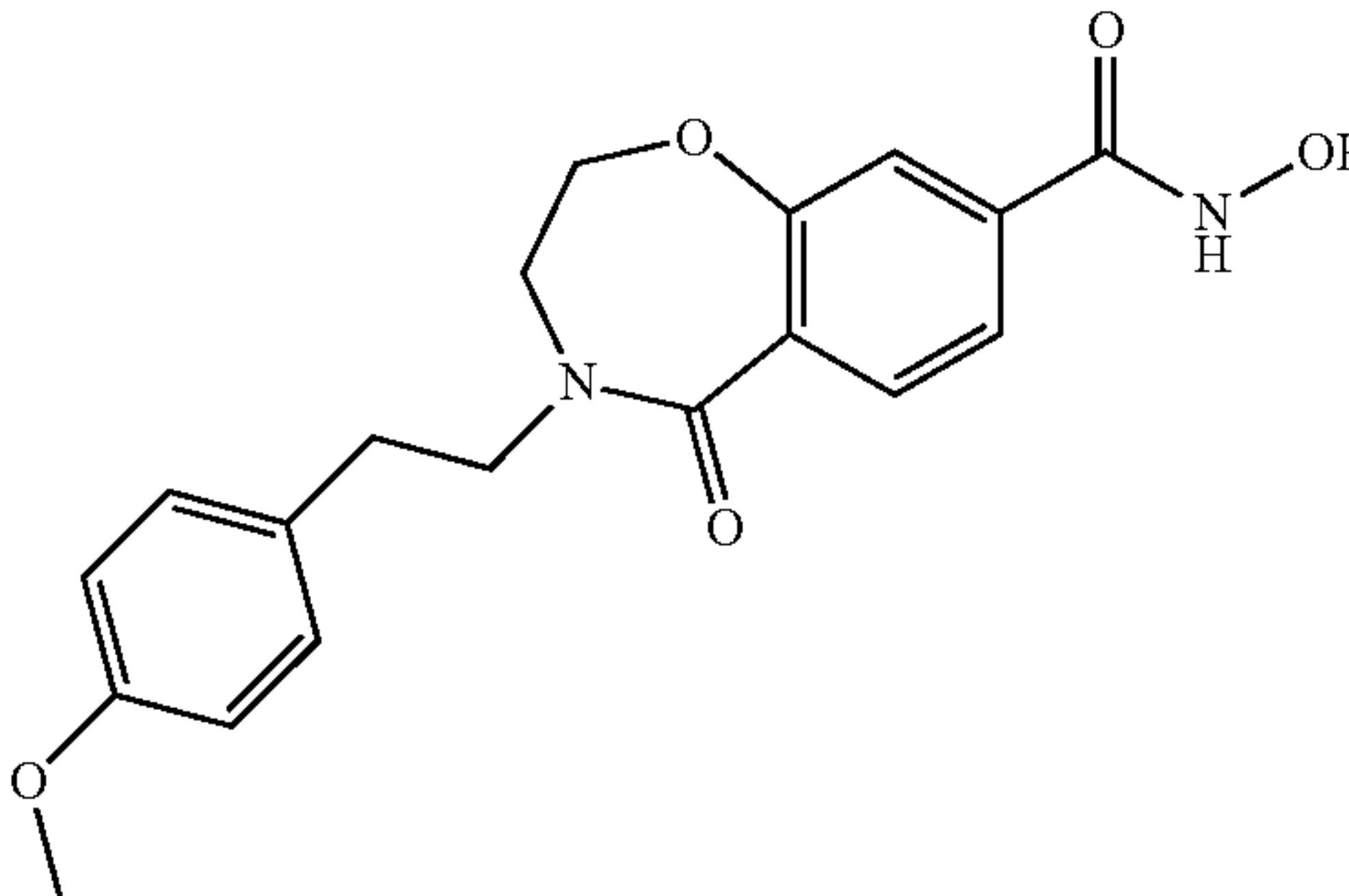


Sodium hydride (60% dispersion in mineral oil, 8.14 mg, 0.203 mmol, 1.5 equiv) was added to a solution of methyl 5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (30 mg, 0.136 mmol, 1 equiv) in DMF (1.4 mL) and the

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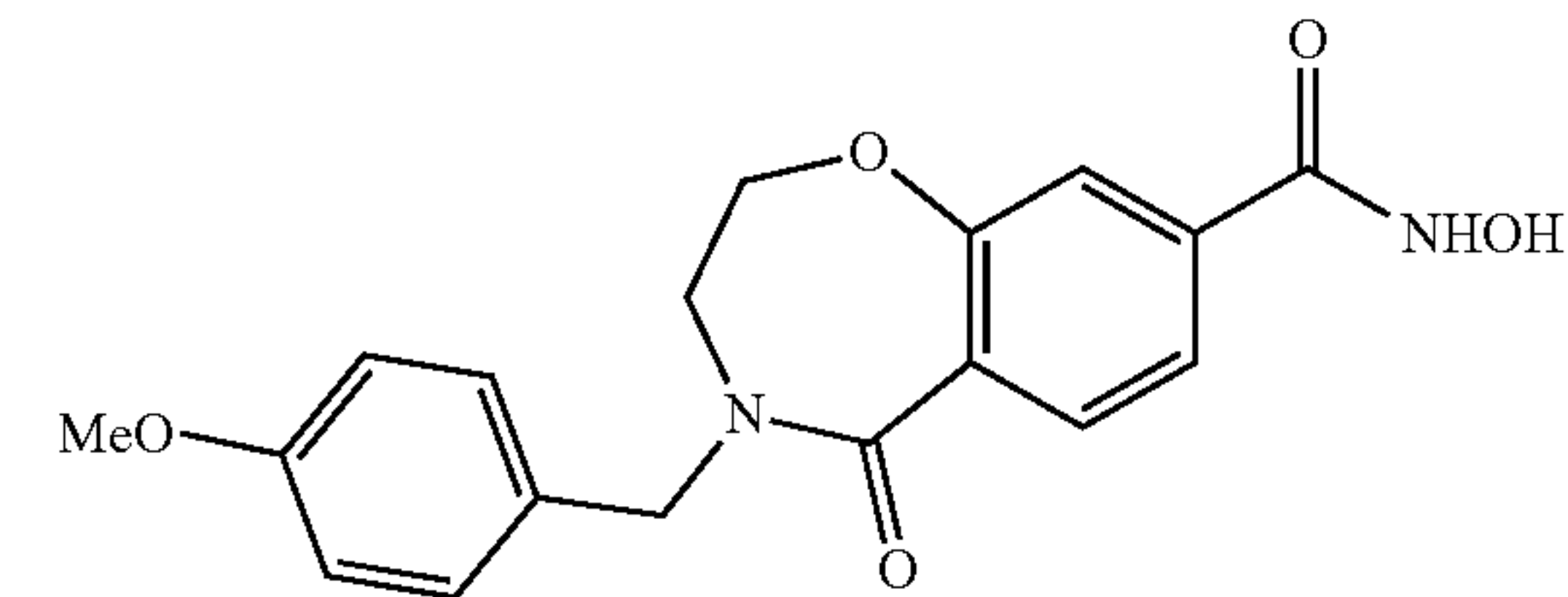
(167  $\mu$ L, 2.72 mmol, 20 equiv) and aqueous 2N NaOH solution (136  $\mu$ L, 0.272 mmol, 2 equiv). The reaction was stirred at room temperature for 2 h. The reaction was acidified with 2N HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by Prep-HPLC (Column: XBridge RP C18 OBD, 5  $\mu$ M, 19 $\times$ 50 mm; Mobile Phase A: Water/0.1% Formic Acid; Mobile Phase B: MeCN/0.1% Formic Acid; Flow rate: 23 mL/min; Gradient: 10% B to 70% B in 7 min) to afford the title compound (22 mg, 47% over 2 steps). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$ (ppm): 11.28 (br s, 1H), 9.15 (br s, 1H), 7.73 (d, J=7.9 Hz, 1H), 7.51 (dd, J=8.1, 1.6 Hz, 1H), 7.15-7.40 (m, 3H), 6.73-7.06 (m, 2H), 4.65 (s, 2H), 4.18 (t, J=5.0 Hz, 2H), 3.68-3.76 (m, 3H), 3.46 (t, J=5.1 Hz, 2H). MS: (ES, m/z): 343 [M+H]<sup>+</sup>.

TABLE 31

The following compound was prepared according to the method of Example 67.		
Structure	Found M + H	<sup>1</sup> H-NMR (300 MHz, DMSO-d <sub>6</sub> ) δ(ppm)
	(ES, m/z): 11.30 (s, 1 H), 9.13 (s, 1 H), 7.66 (d, J = 7.9 Hz, 1 H), 357 7.48 (dd, J = 8.1, 1.6 Hz, 1 H), 7.32 (d, J = 1.5 Hz, 1 H), [M + H] <sup>+</sup> 7.16 (m, J = 8.8 Hz, 2 H), 6.79-6.89 (m, 2 H), 4.24 (t, J = 5.0 Hz, 2 H), 3.64-3.72 (m, 5 H), 3.46 (br t, J = 5.0 Hz, 2 H), 2.73-2.84 (m, 2 H)	

solution was stirred at room temperature for 30 minutes. 1-(Bromomethyl)-4-methoxybenzene (57  $\mu$ L, 0.407 mmol, 3 equiv) was added and the reaction was stirred at 50° C. overnight. The reaction mixture was partitioned between EtOAc and saturated aqueous solution of NaHCO<sub>3</sub>. The layers were separated and the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (Gradient 20-80% EtOAc/hexanes) to afford the title compound as a colorless oil.

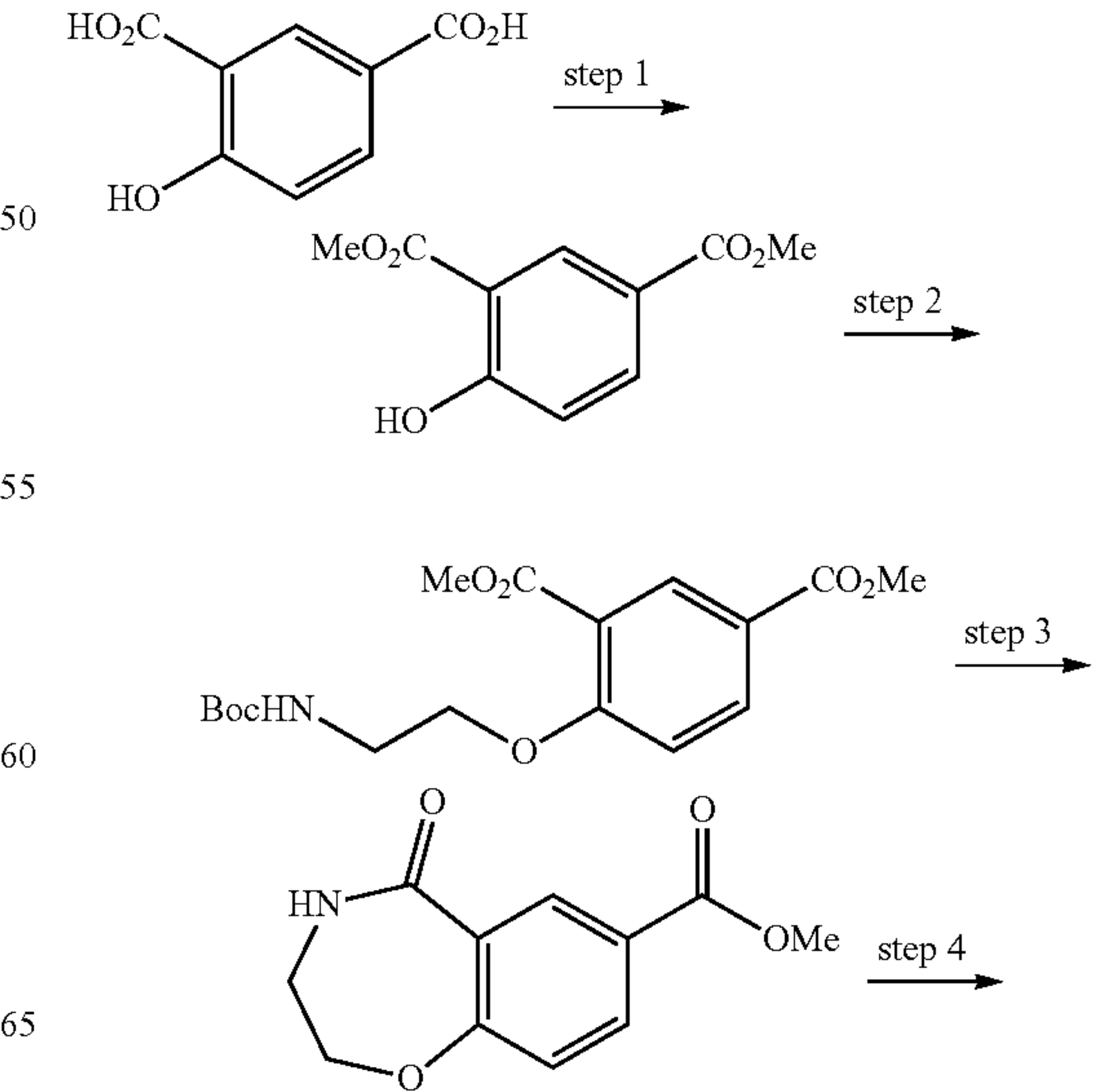
Step-6: N-Hydroxy-4-(4-methoxybenzyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



To a solution of methyl 4-(4-methoxybenzyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (46 mg, 0.136 mmol, 1 equiv) in MeOH (272  $\mu$ L) and THF (1 mL) was added an aqueous 50% wt hydroxylamine solution

Example 68

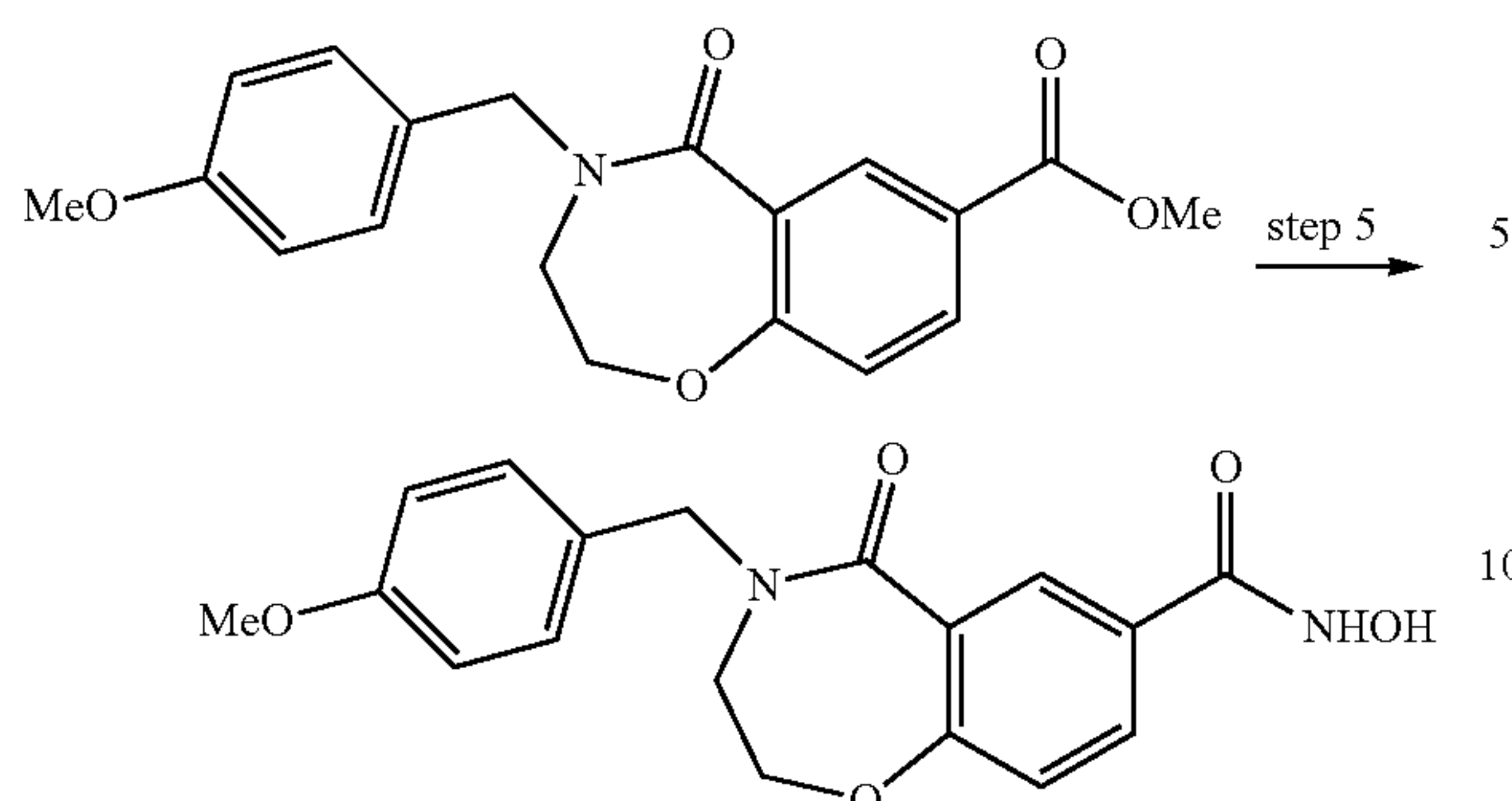
Preparation of N-Hydroxy-4-(4-methoxybenzyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide



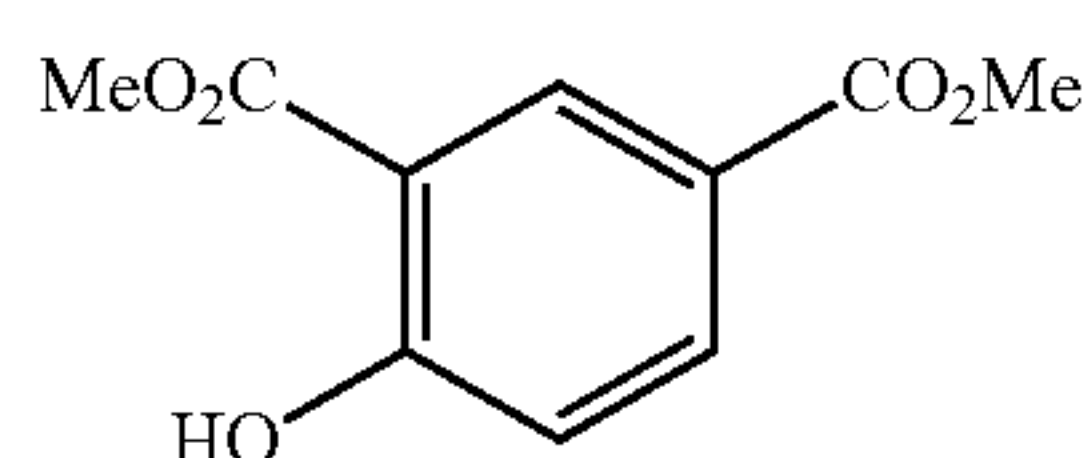


**203**

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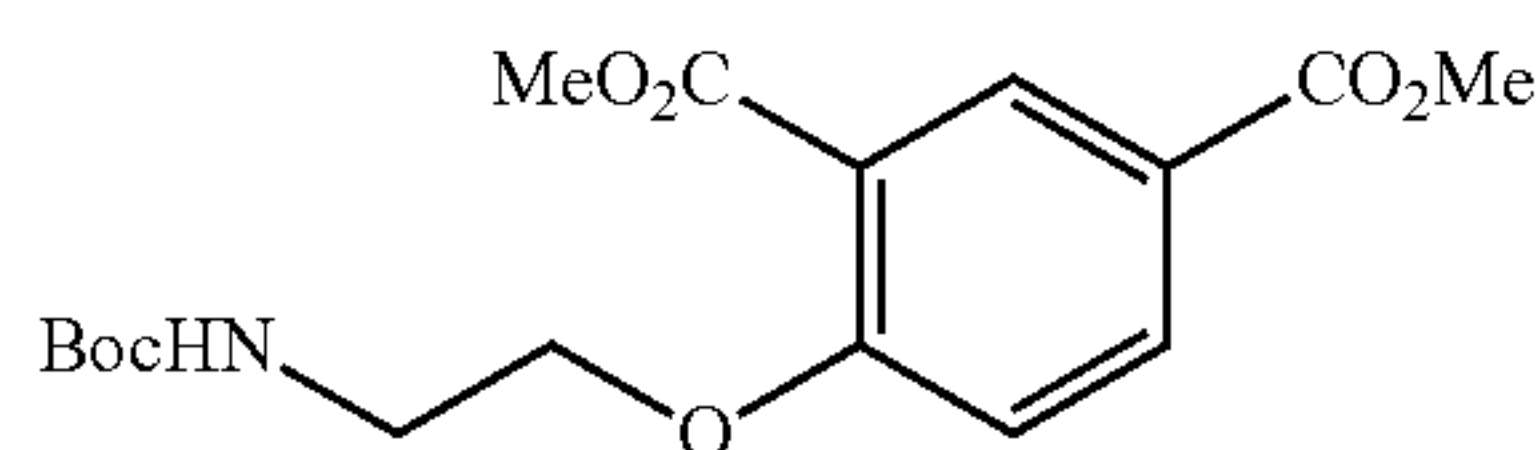


Step-1: Dimethyl 4-hydroxyisophthalate



Under a nitrogen purge, 4-hydroxyisophthalic acid (10.9 g, 0.06 mol) was dissolved in MeOH (85 mL) in a 250 mL 3-neck round-bottomed flask. Sulfuric acid (98%, 8.5 mL) was placed in an addition funnel and added dropwise over 25 min, resulting in an exotherm to 35° C. After the addition was completed, the reaction was heated to a gentle reflux, and maintained for 28 h. Upon removal of heat source, a white precipitate began to form. The flask was further cooled in an ice bath, and the solids were then isolated by filtration. The solid was washed with cold isopropanol and then with hexanes, and then allowed to dry on the filter, providing the title compound as a white solid (10.4 g, 82% yield).

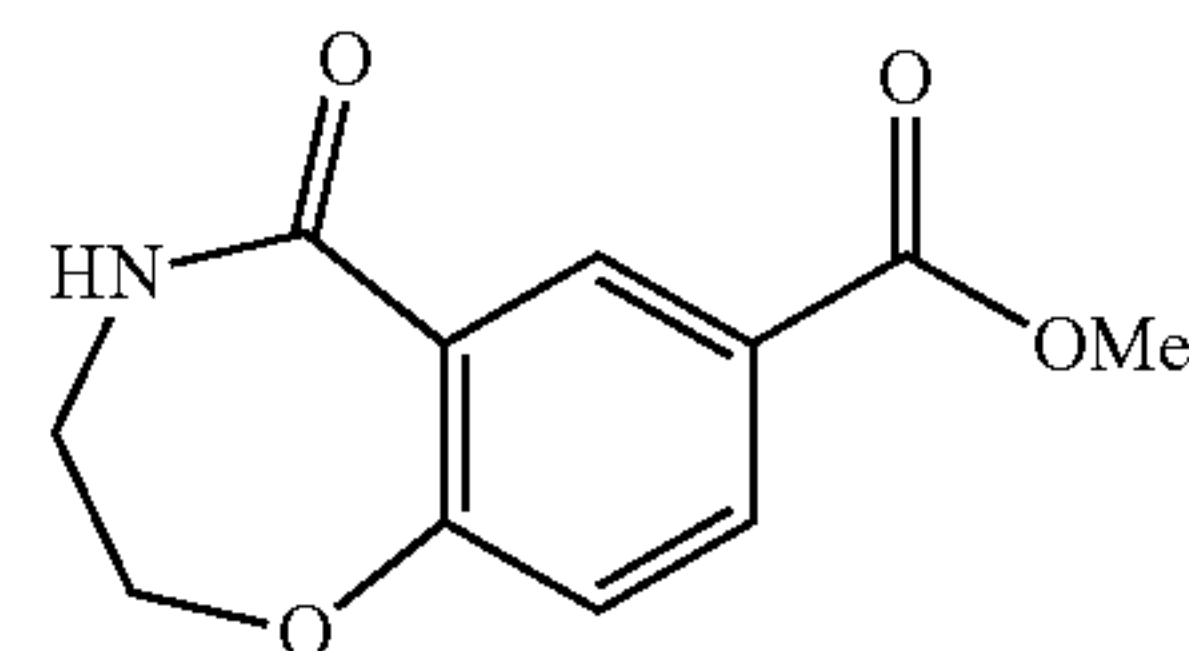
Step-2: Dimethyl 4-(2-((tert-butoxycarbonyl)amino)ethoxy)isophthalate



Under a nitrogen purge, dimethyl 4-hydroxyisophthalate (2.10 g 0.01 mol) was dissolved in MeCN (70 mL) in a 250 mL 3-neck round-bottomed flask. 18-Crown-6 (0.13 g, 5 mol %) and potassium carbonate (1.5 g, 0.011 mol) were added sequentially, in single portions, washing in with MeCN (10 mL). Tert-butyl(2-bromoethyl)carbamate (2.24 g, 0.01 mol) was added in a single portion, and washed in with MeCN (5 mL). The resulting suspension was heated at reflux for 16 h. Heat was removed, and the reaction mixture was cooled in an ice/acetone bath. Solids were removed by filtration, and the filter cake was washed with more MeCN. The filtrate was pre-absorbed directly onto silica gel, and purified by silica gel chromatography (Gradient 15-50% EtOAc/hexanes) to afford the title compound as an amber oil which slowly solidified (1.1 g, 31% yield).

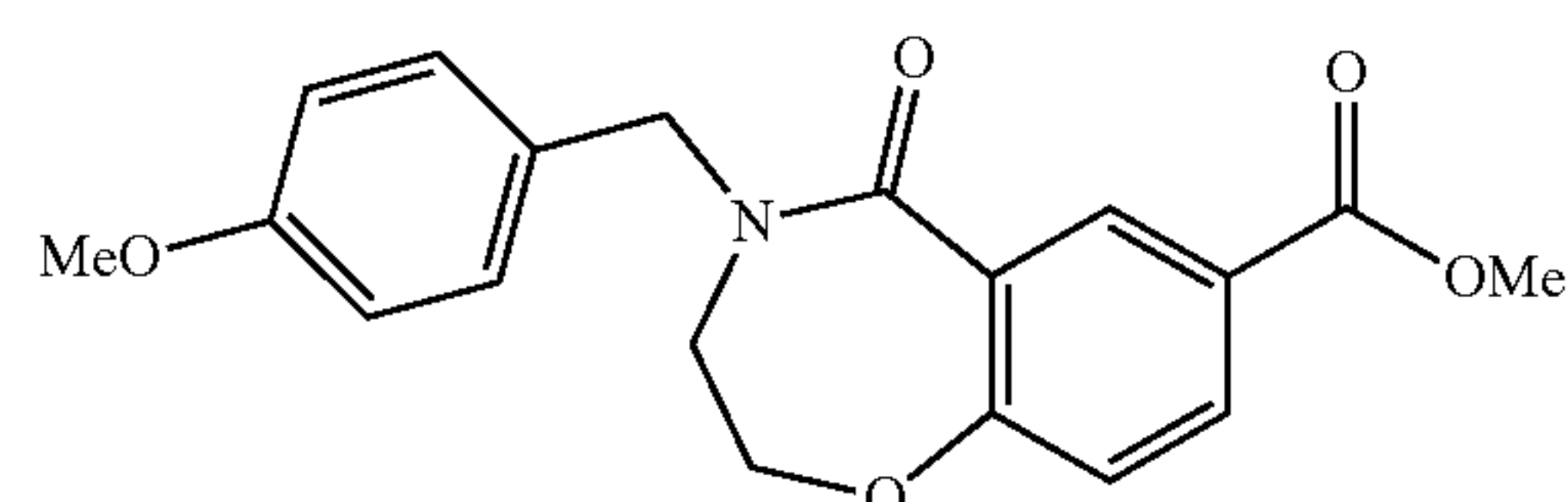
**204**

Step-3: Methyl 5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate



Dimethyl 4-(2-((tert-butoxycarbonyl)amino)ethoxy)isophthalate (2.2 g, 6.2 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) in a 50 mL round-bottomed flask. TFA (4 mL) was added in a single portion, and the resulting solution was stirred for 16 h. Solvent was removed under reduced pressure to provide an oil. Five times, toluene was added and removed under reduced pressure. The resulting solid was suspended in toluene (40 mL), and Et<sub>3</sub>N (3.5 mL, 0.025 mol) was added in a single portion. Upon heating to reflux, all solids slowly dissolved to provide a clear solution. The reaction was heated for another 16 h, then partitioned between EtOAc and water. The organic layer was washed with water and brine, dried over MgSO<sub>4</sub>, filtered and concentrated. Purification by recrystallization from 2-propanol afforded the title compound as a pale beige solid (0.65 g, 47% yield). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ(ppm): 3.54-3.61 (m, 2H) 3.90 (s, 3H) 4.45-4.51 (m, 2H) 7.04 (d, J=8.53 Hz, 1H) 7.42 (br. s., 1H) 8.07 (dd, J=8.53, 2.20 Hz, 1H) 8.76 (d, J=2.20 Hz, 1H).

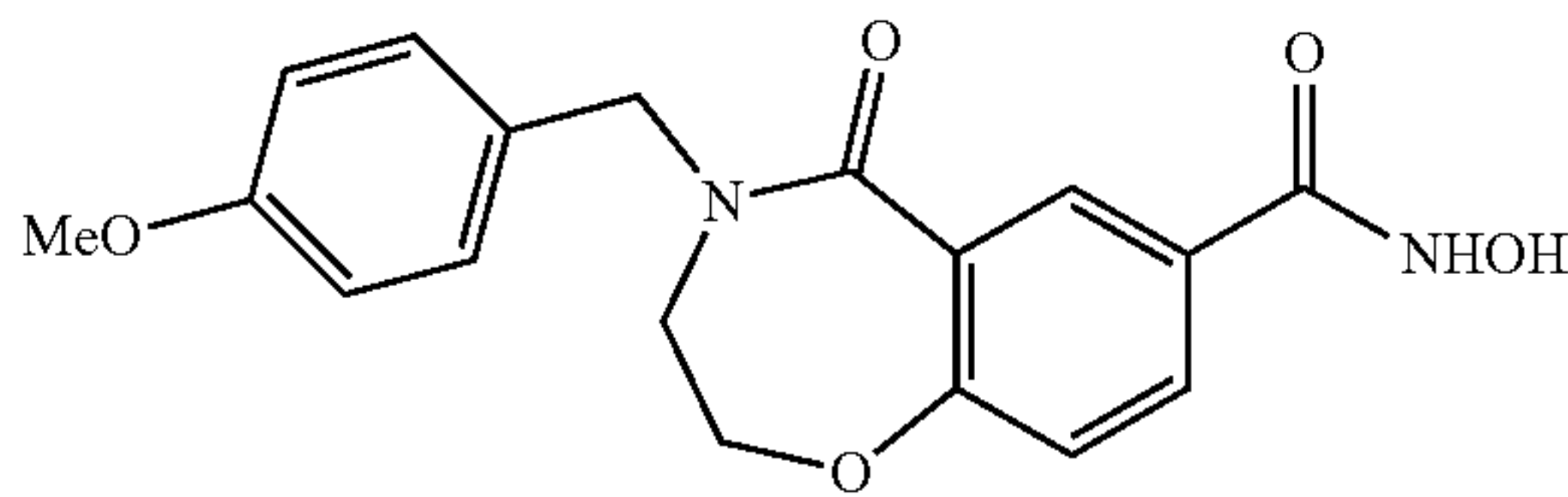
Step-4: Methyl 4-(4-methoxybenzyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate



Sodium hydride (60% dispersion in mineral oil, 13 mg, 0.325 mmol, 1.5 equiv) was added to a solution of methyl 5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate (48 mg, 0.217 mmol, 1 equiv) in DMF (2.2 mL) and the solution was stirred at room temperature for 30 minutes. 1-(Bromomethyl)-4-methoxybenzene (33.5 μL, 0.239 mmol, 1.1 equiv) was added and the reaction was stirred at 50° C. overnight. The reaction mixture was partitioned between EtOAc and saturated aqueous solution of NaHCO<sub>3</sub>. The layers were separated and the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (Gradient 20-80% EtOAc/hexanes) to afford the title compound as a white solid (33 mg, 45% yield). MS: (ES, m/z): 342 [M+H]<sup>+</sup>.

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Step-5: N-Hydroxy-4-(4-methoxybenzyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide



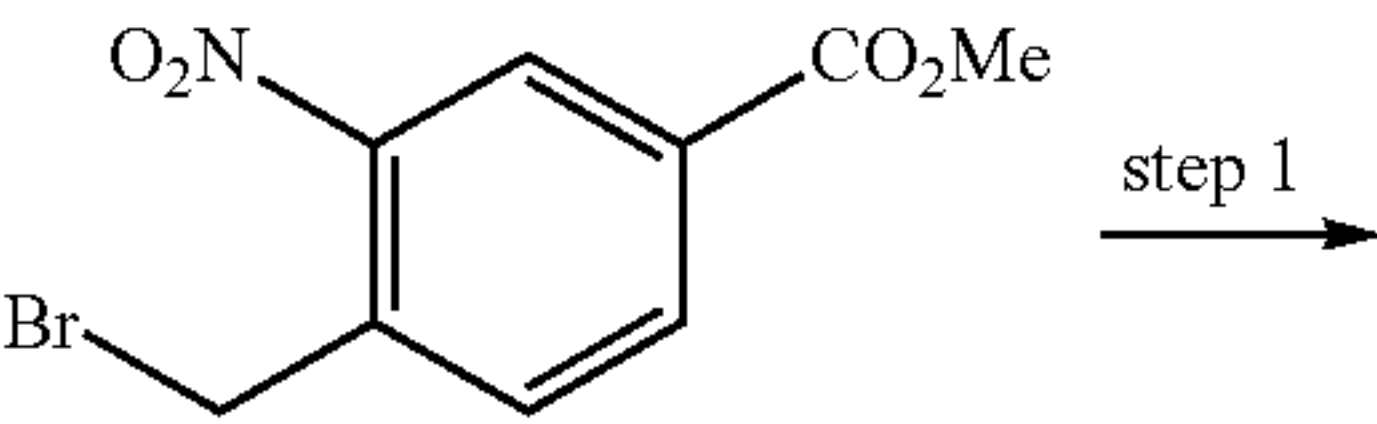
To a solution of methyl 4-(4-methoxybenzyl)-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate (33 mg, 0.097 mmol, 1 equiv) in MeOH (152  $\mu$ L) and THF (608  $\mu$ L) was added  $\text{NH}_2\text{OH}$  (50% in water, 118  $\mu$ L, 1.94 mmol, 20 equiv) and aq. 2N NaOH (97  $\mu$ L, 0.194 mmol, 2 equiv). The reaction was stirred at room temperature for 3 days. The reaction was directly purified by Prep-HPLC (Column: XBridge RP C18 OBD, 5  $\mu$ M, 19 $\times$ 50 mm; Mobile Phase A: Water/0.1% Formic Acid; Mobile Phase B: MeCN/0.1% Formic Acid; Flow rate: 23 mL/min; Gradient: 10% B to 70% B in 7 min) to afford the title compound as an oil (3.5 mg, 13% yield).  $^1\text{H-NMR}$  (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 10.3 (s, 1H), 8.33 (s, 1H), 8.15 (s, 1H), 7.83-7.76 (m, 1H), 7.25 (br d,  $J=7.3$  Hz, 2 H), 7.03 (br d,  $J=8.5$  Hz, 1 H), 6.89 (br d,  $J=8.5$  Hz, 2 H), 4.65 (s, 2 H), 4.22 (br s, 2 H), 3.71 (s, 3 H), 3.48 (br s, 2 H). MS: (ES,  $m/z$ ): 343  $[\text{M}+\text{H}]^+$ .

TABLE 32

The following compound was prepared according to the method of Example 68.		
Structure	Found M + H	$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-d}_6$ ) $\delta$ (ppm)
	(ES, $m/z$ ): 357 $[\text{M} + \text{H}]^+$	

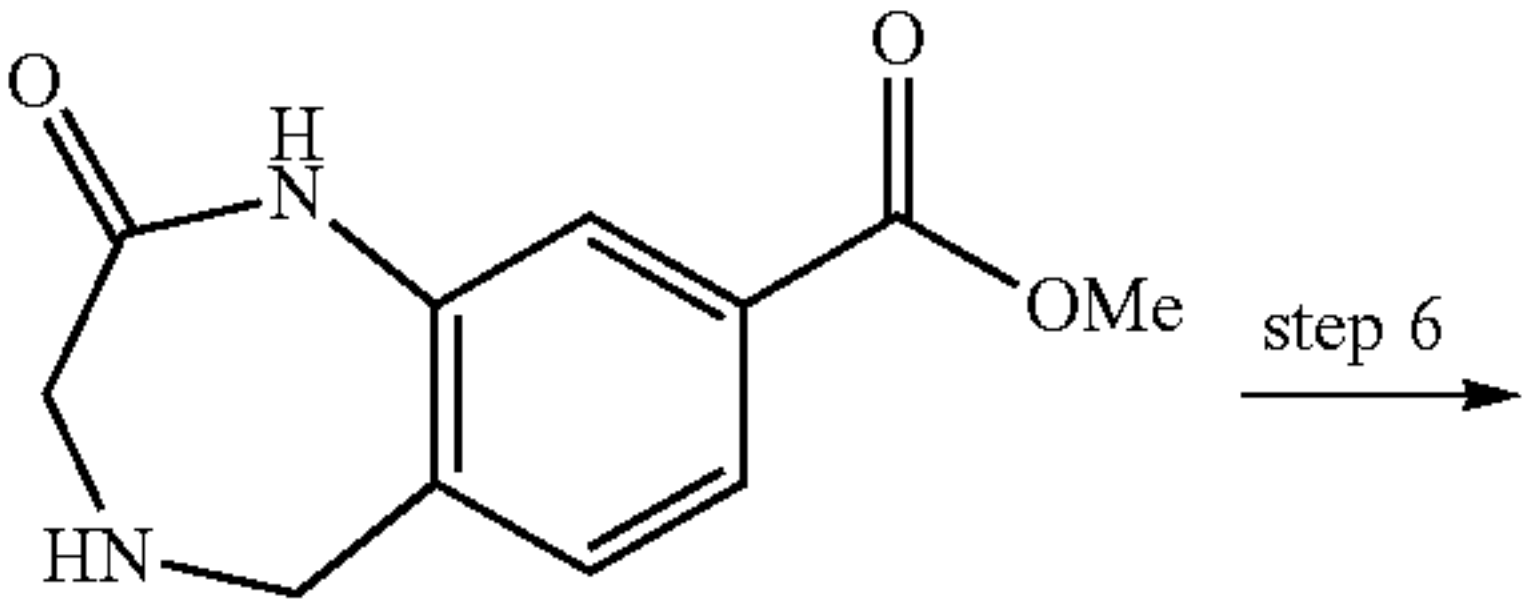
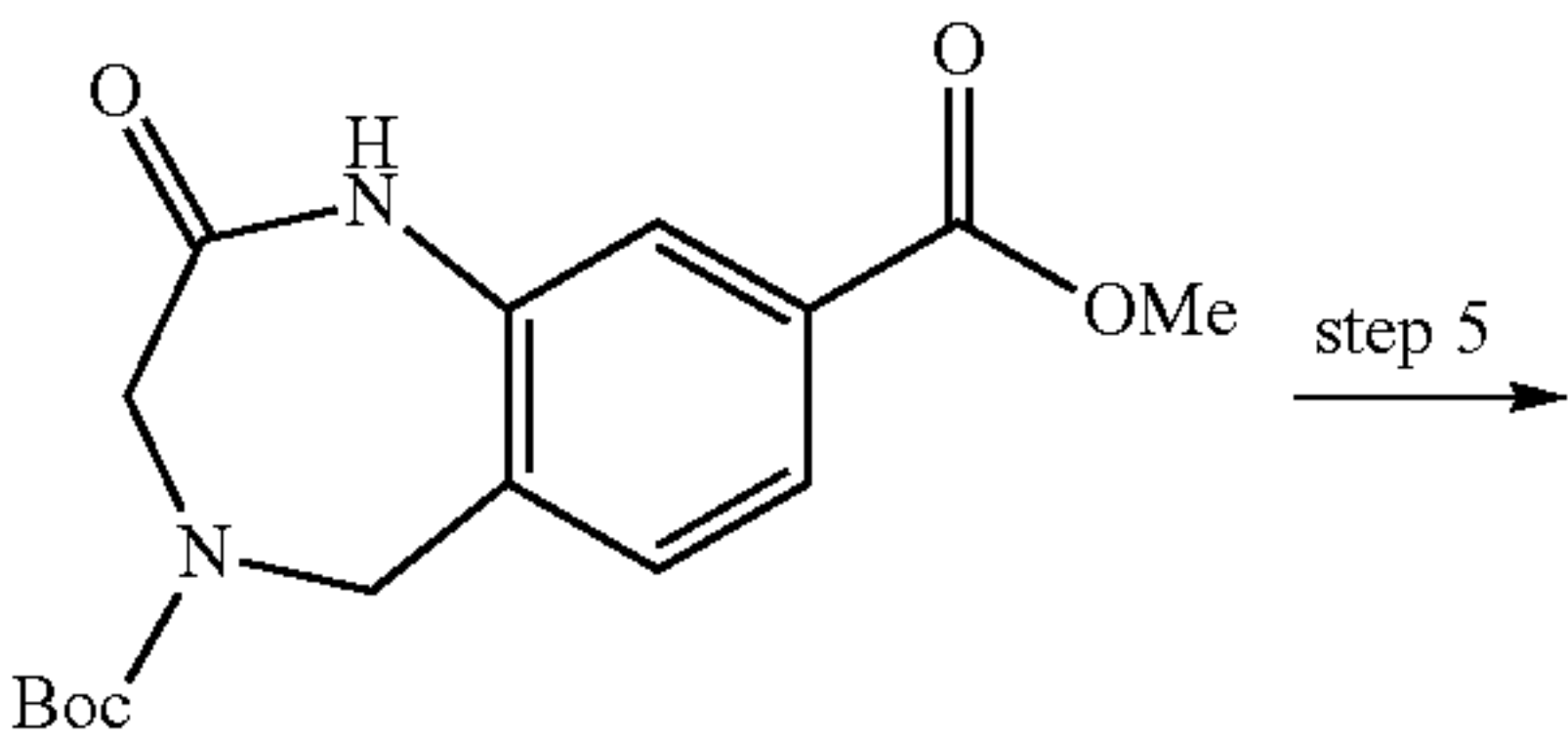
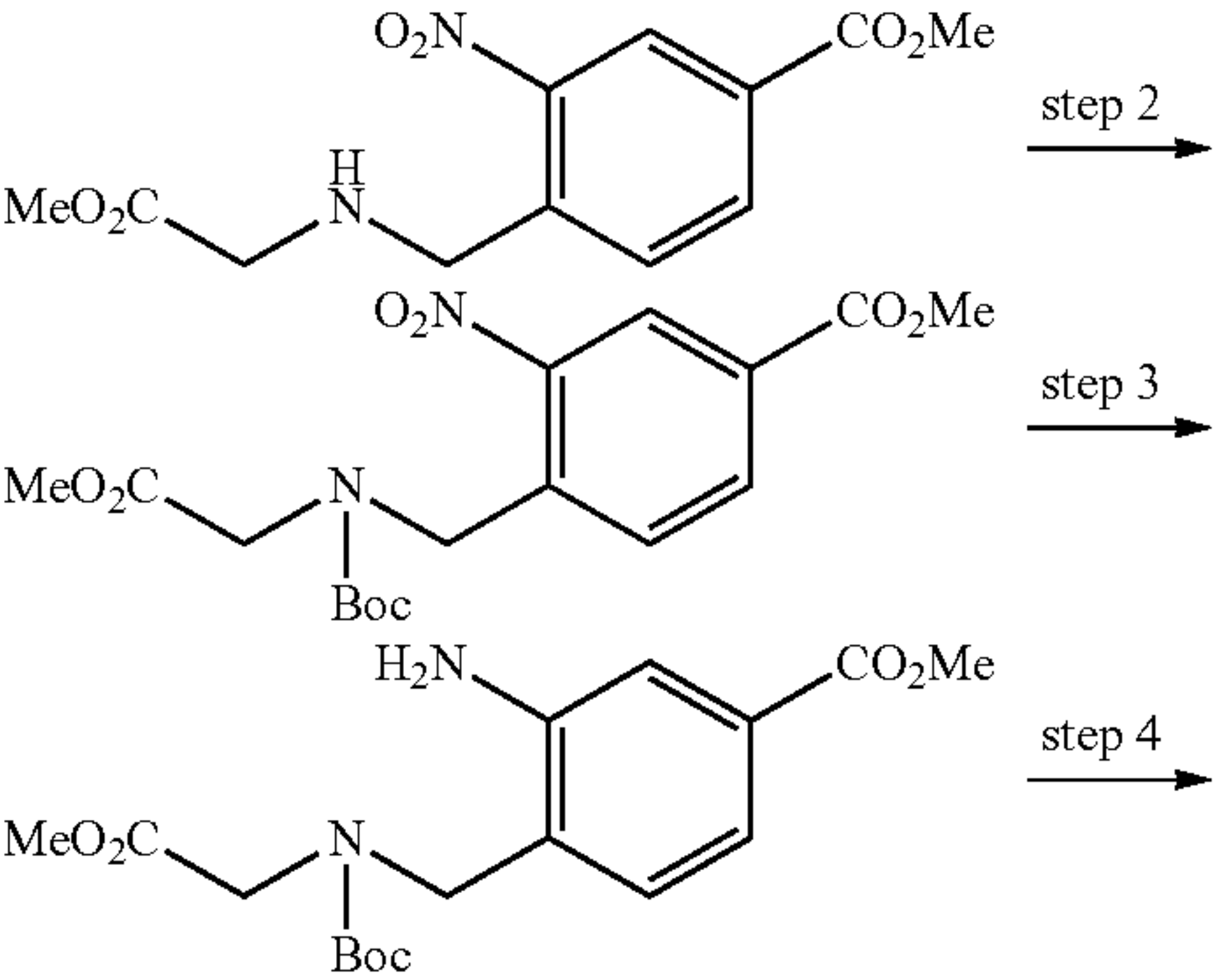
Example 69

Preparation of N-hydroxy-4-(4-methoxyphenethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-8-carboxamide

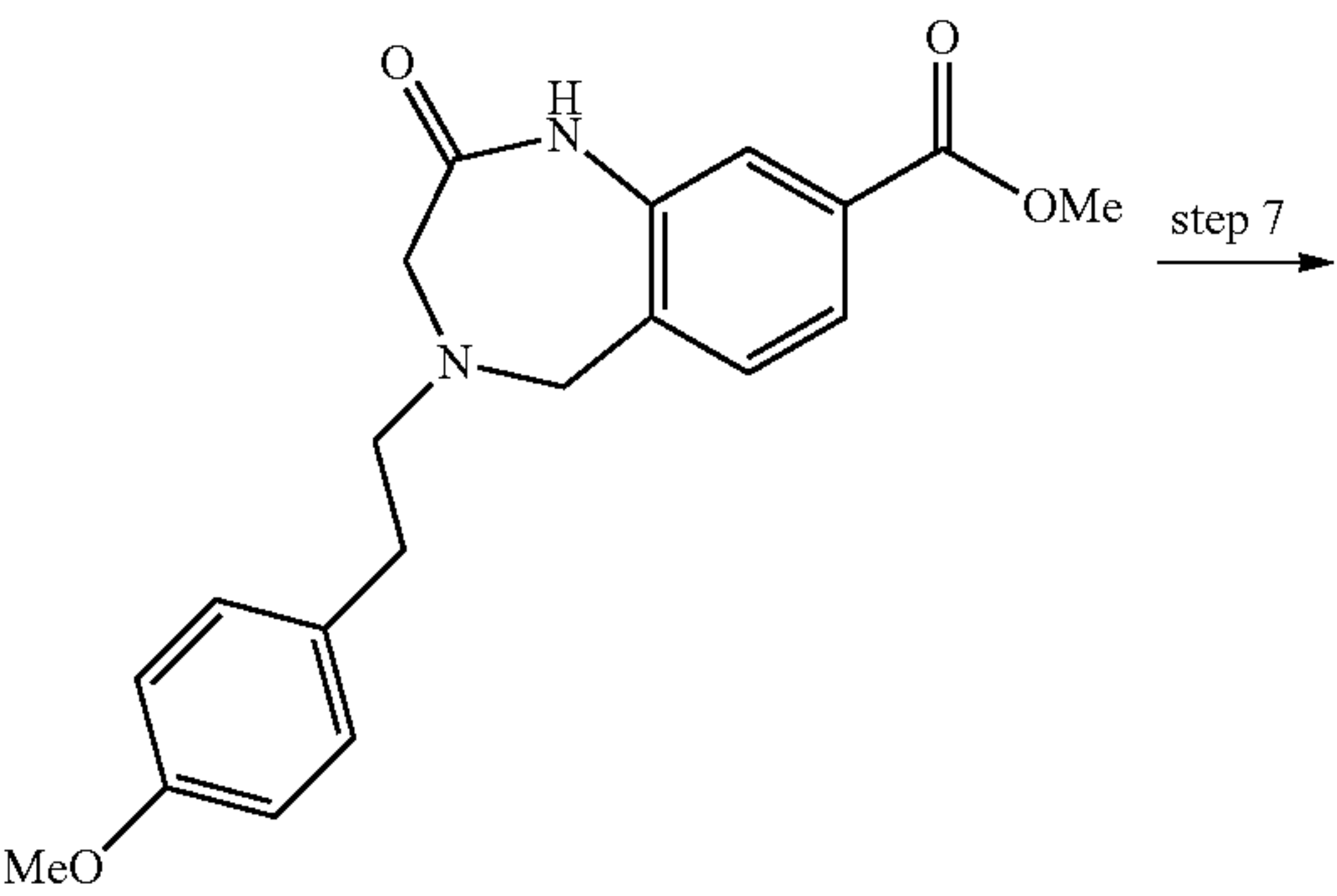


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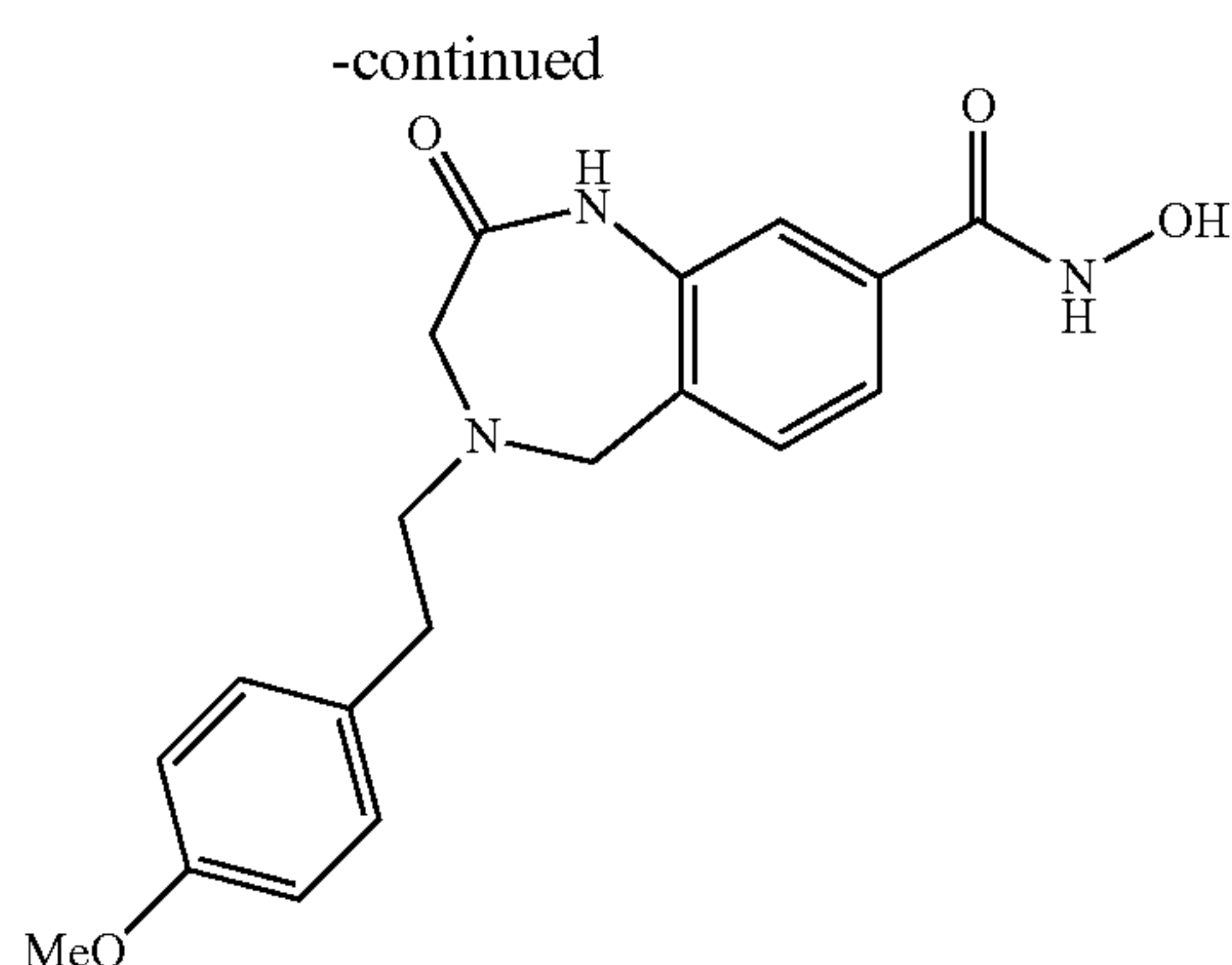
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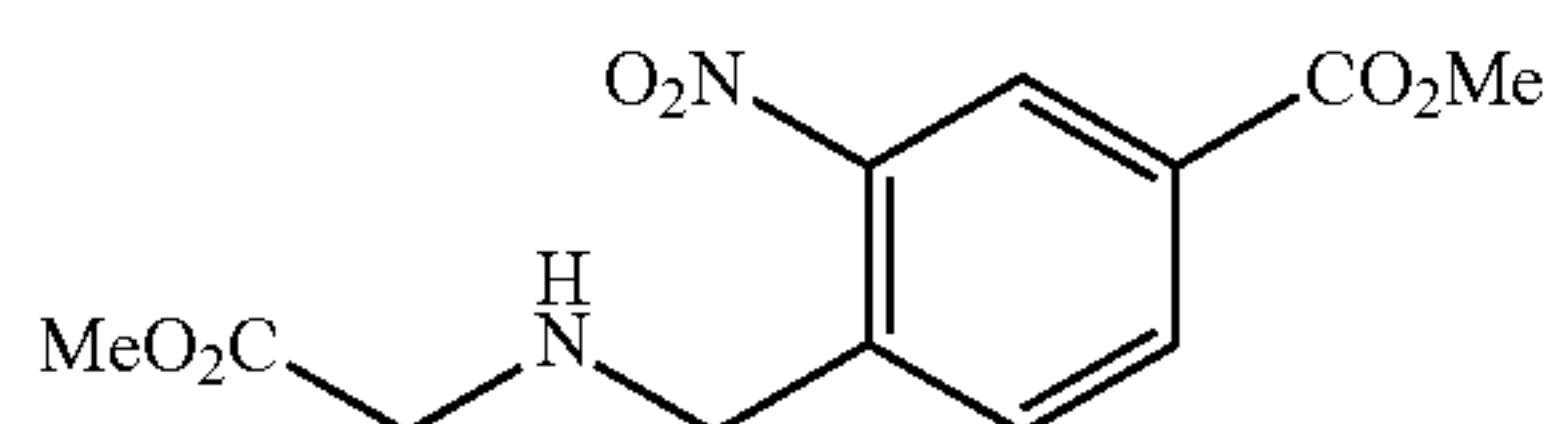
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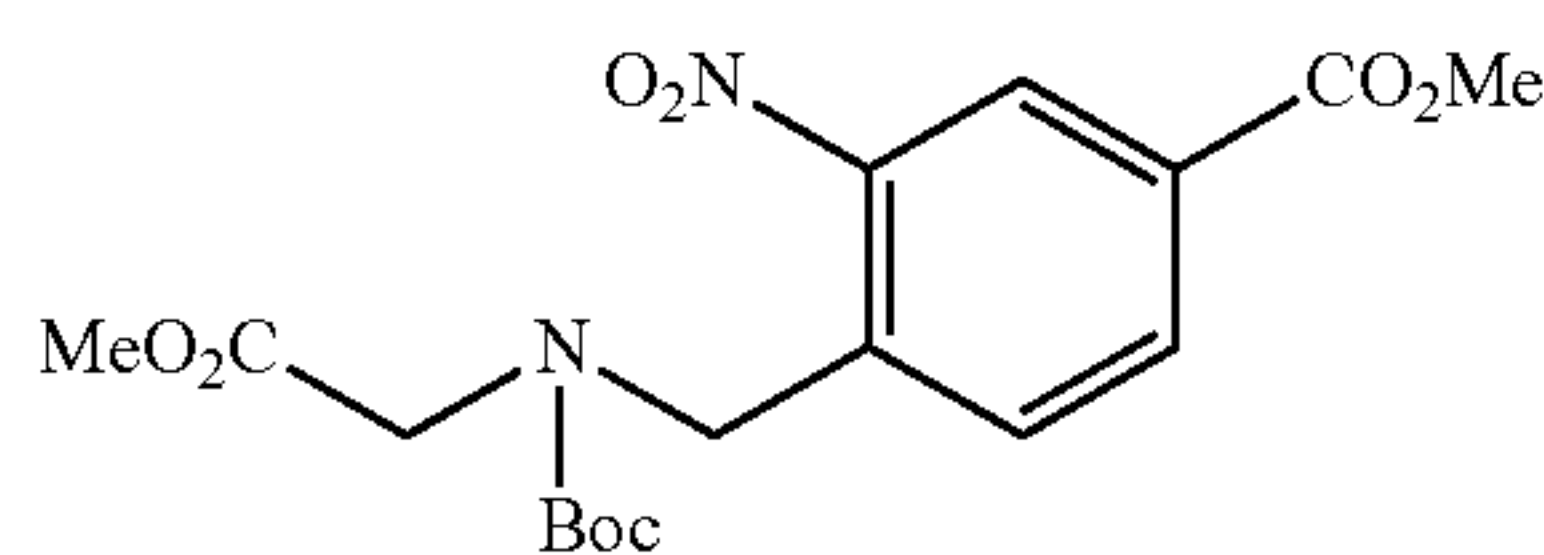
**207**

Step-1: Methyl 4-(((2-methoxy-2-oxoethyl)amino)methyl)-3-nitrobenzoate



To a solution of methyl 4-(bromomethyl)-3-nitrobenzoate (5.2 g, crude, 18.3 mmol) and methyl 2-aminoacetate hydrochloride (6.86 g, 54.9 mmol) in DMF (15 mL) stirred at room temperature, was added DIEA (12.7 mL, 73.2 mmol) dropwise. After 5 hours, it was diluted with Et<sub>2</sub>O (120 mL), washed with water (3×80 mL) and brine (80 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The brown solid residue was purified by silica gel chromatography (Gradient 0-100% EtOAc/hexanes) to give the title compound (4.2 g)

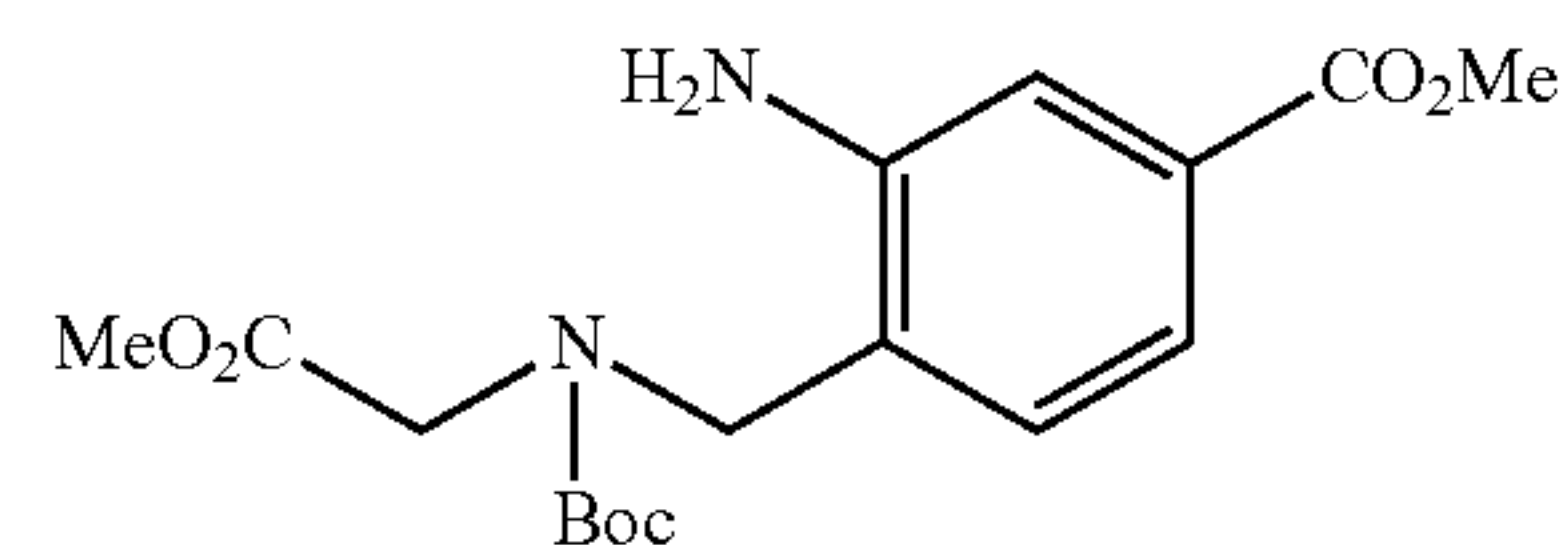
Step-2: Methyl 4-(((tert-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)methyl)-3-nitrobenzoate



To a solution of methyl 4-(((2-methoxy-2-oxoethyl)amino)methyl)-3-nitrobenzoate (4.2 g, 15 mmol) in EtOAc/hexanes (200 mL, 1:1) stirred at room temperature, was added di-tert-butyl dicarbonate (3.4 g, 15.6 mmol) followed by 4-dimethylaminopyridine (50 mg). The reaction was stirred at room temperature overnight. TLC indicated there was still a lot of starting material. More di-tert-butyl dicarbonate (2.0 g, 9.2 mmol) was added and the mixture was stirred for another 3 hours. It was concentrated under reduced pressure. The residue was purified by silica gel chromatography (Gradient 0-100% EtOAc/hexanes) to give the title compound as a yellow oil (4.9 g, 70% yield over 3 steps).

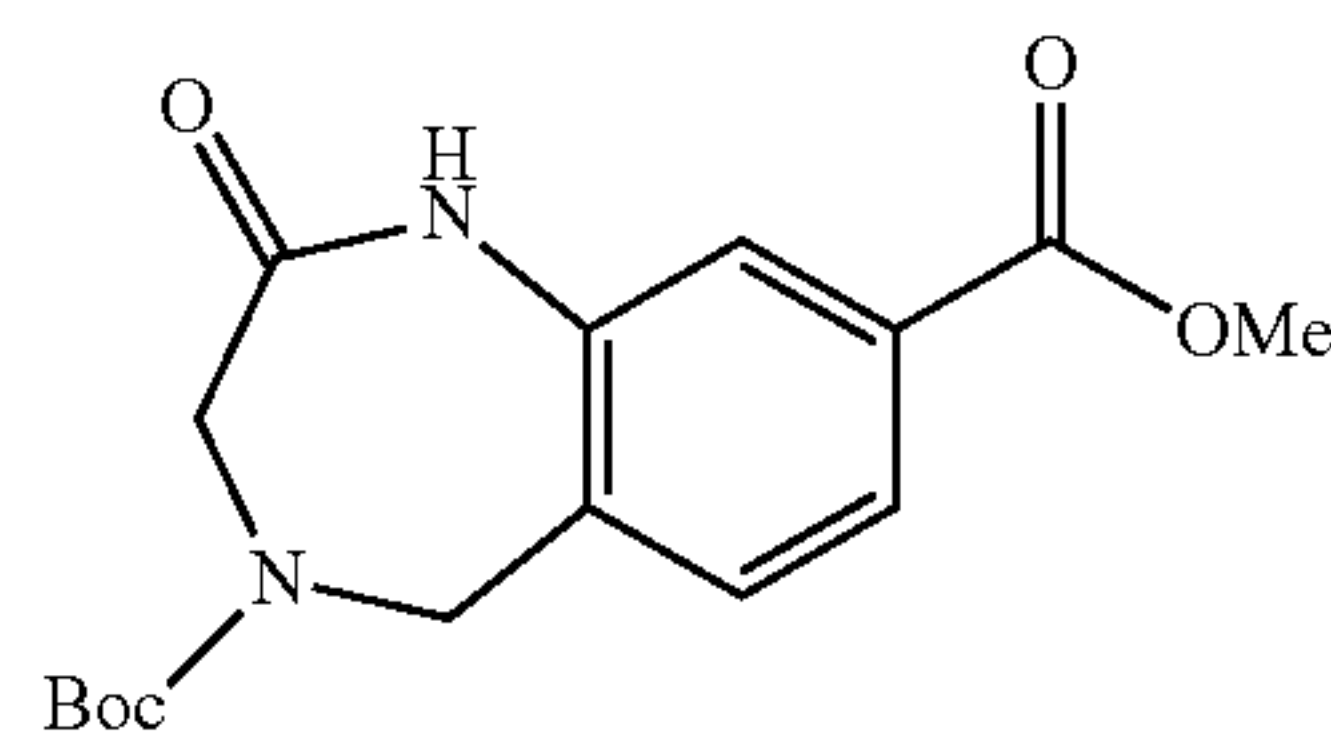
**208**

Step-3: Methyl 3-amino-4-(((tert-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)methyl)benzoate



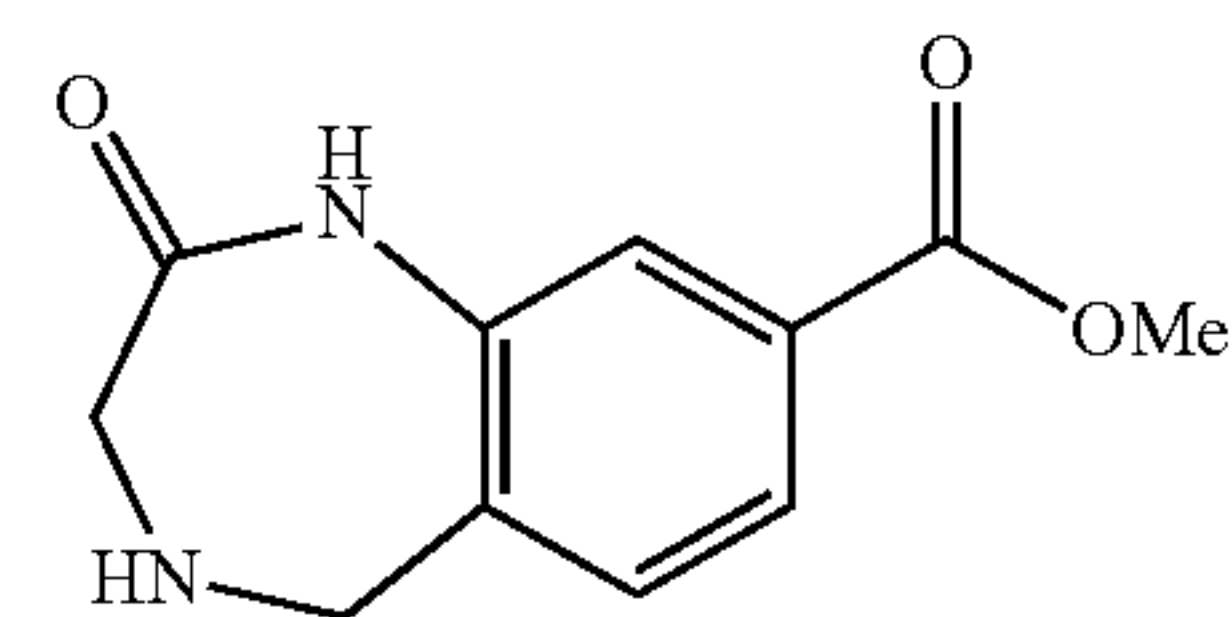
To a solution of methyl 4-(((tert-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)methyl)-3-nitrobenzoate (4.9 g, 12.8 mmol) in MeOH (100 mL) was added 10% Pd/C (2.5 g). The mixture was purged with N<sub>2</sub> for 10 min and then stirred under a hydrogen balloon for 16 h. The mixture was filtered through Celite and the filtrate was evaporated under reduced pressure to give the title compound as a greenish gum (4.0 g, 89% yield).

Step-4: 4-(tert-Butyl) 8-methyl 2-oxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4,8-dicarboxylate



A solution of methyl 3-amino-4-(((tert-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)methyl)-benzoate (4.0 g, 13 mmol) in anhydrous toluene (100 mL) was stirred under reflux overnight. After removal of solvent under reduced pressure, the residue was purified by silica gel chromatography (Gradient 10-100% EtOAc/hexanes) to give the title compound as an off-white solid (0.96 g, 27% yield).

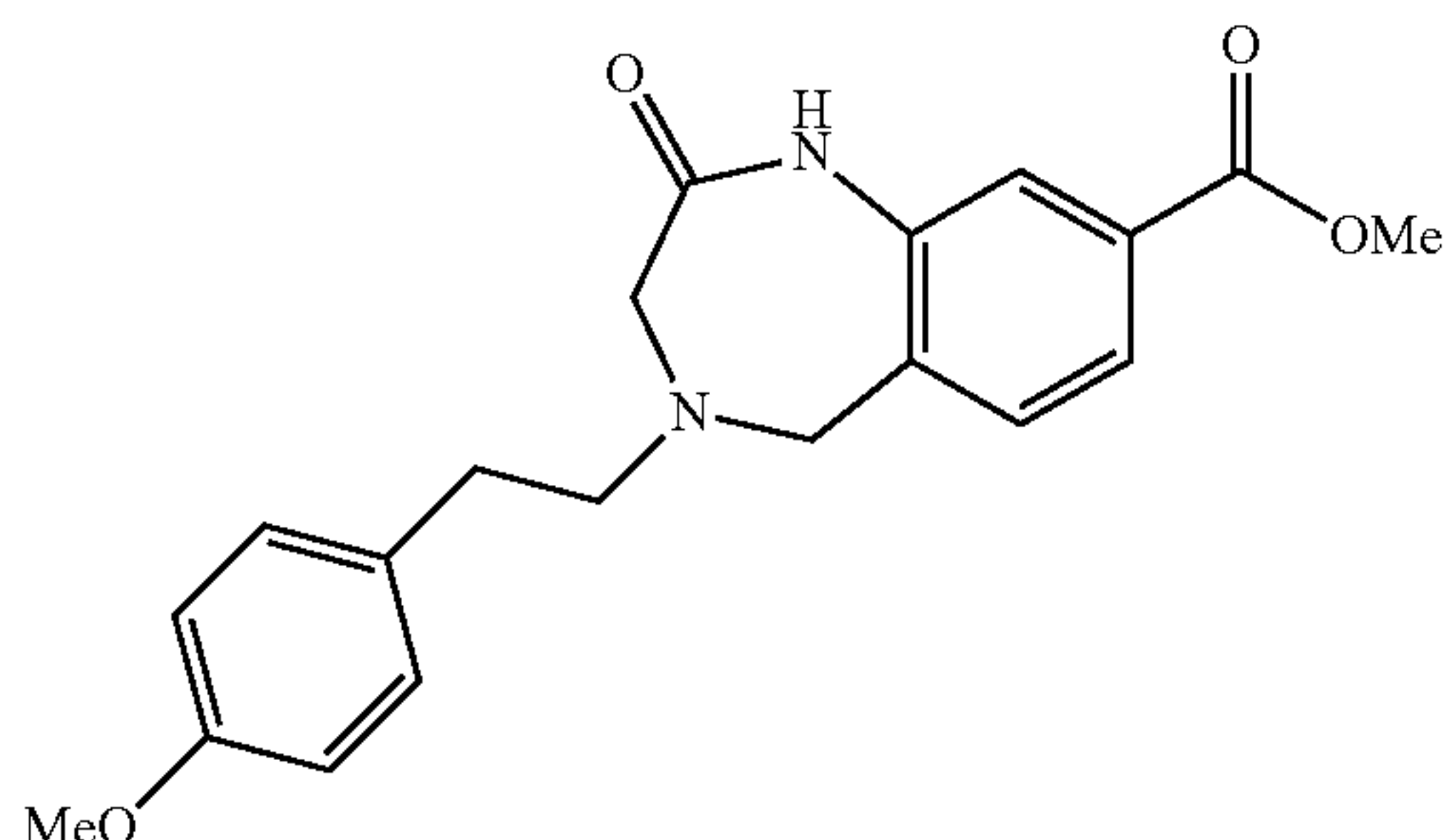
Step-5: Methyl 2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-8-carboxylate



To a solution of HCl in dioxane (4M, 30 mL) was added 4-(tert-butyl) 8-methyl 2-oxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4,8-dicarboxylate (956 mg, 2.98 mmol). The mixture was stirred at room temperature for 5 hours. The solid precipitates were collected by filtration and dried at 50° C. under vacuum overnight to give the title compound as its HCl salt as an off-white solid (745 mg, 97% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 10.69 (s, 1H), 10.17 (s, 1H), 7.79 (dd, J=7.7, 1.5 Hz, 1H), 7.70 (d, J=1.6 Hz, 1H), 7.60 (d, J=7.7 Hz, 1H), 4.28 (s, 2H), 3.88 (s, 3H), 3.65 (s, 2H). MS: (APCI, m/z): 221 [M-Cl]<sup>+</sup>.

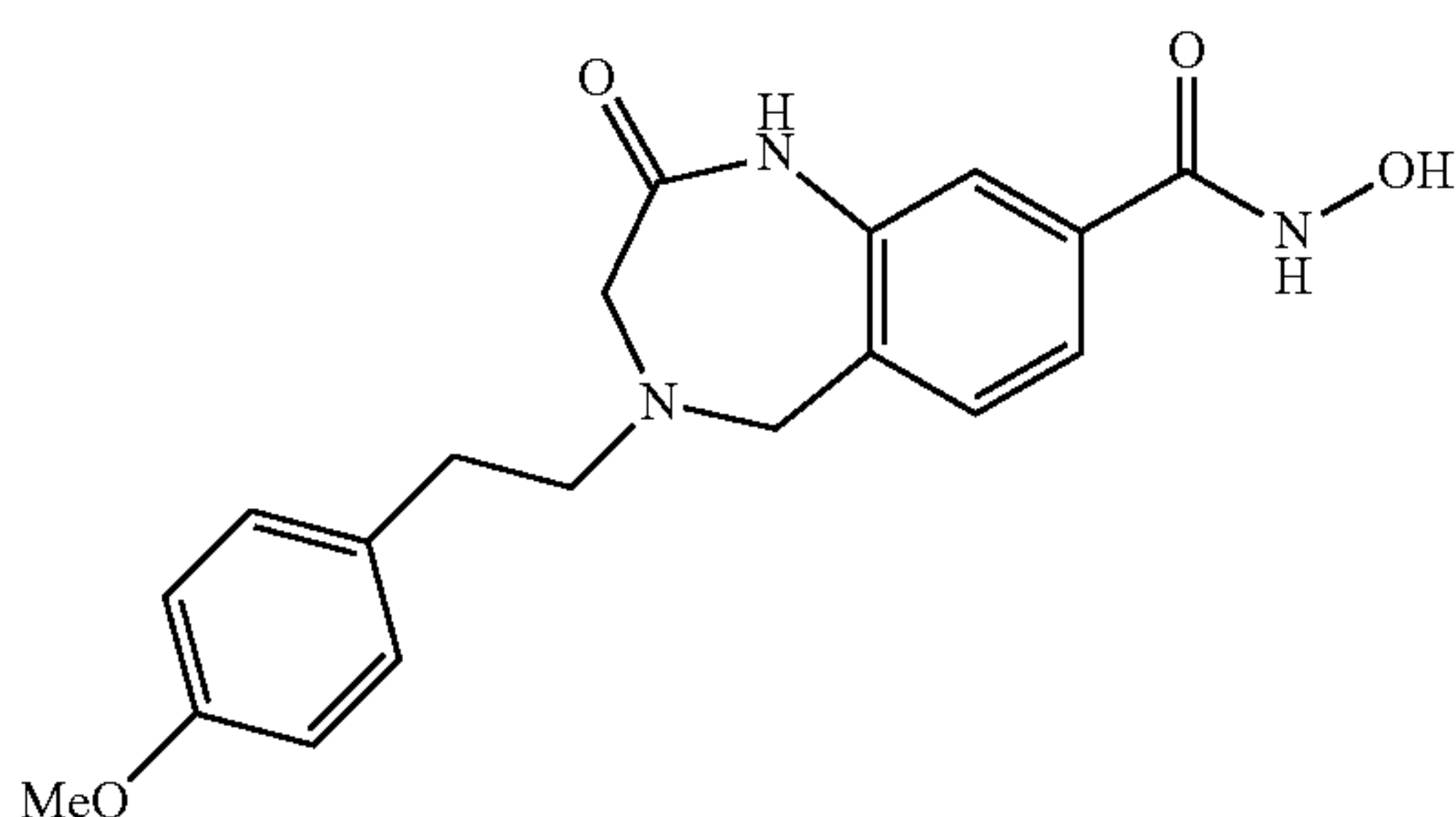
## 209

Step-6: Methyl 4-(4-methoxyphenethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-8-carboxylate



To a suspension of methyl 2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-8-carboxylate hydrochloride (40 mg, 0.16 mmol, 1 equiv) and  $K_2CO_3$  (43 mg, 0.31 mmol, 2 equiv) in MeOH was added 1-(2-bromoethyl)-4-methoxybenzene (76  $\mu$ L, 0.49 mmol, 3 equiv). The resulting mixture was heated at 55° C. for 2 days. The reaction mixture was partitioned between EtOAc and a saturated aqueous solution of  $NaHCO_3$ . The layers were separated. The organic layer was washed with water, then with brine, and dried over anhydrous  $Na_2SO_4$ . The solution was filtered, and concentrated. This crude material was purified by silica gel chromatography (Gradient 0-10% MeOH/ $CH_2Cl_2$  with 0.1% formic acid) to afford the title compound as a colorless oil (14.4 mg, 26% yield). MS: (ES, m/z): 355  $[M+H]^+$ .

Step-7: N-Hydroxy-4-(4-methoxyphenethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-8-carboxamide



To a solution of methyl 4-(4-methoxyphenethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-8-carboxylate (14 mg, 0.041 mmol, 1 equiv) in a MeOH/THF (1 mL, 1/4) was added an  $NH_2OH$  (50% in water, 212  $\mu$ L, 3.5 mmol, 85 equiv) and aq. 2N NaOH solution (40.6  $\mu$ L, 0.081 mmol, 2 equiv). The reaction was stirred at room temperature for 2 h, then was acidified with 2N HCl. The mixture was extracted with EtOAc and the separated organic layer was washed with brine, then dried over anhydrous  $Na_2SO_4$ . The solution was filtered, and concentrated. This crude material was purified by Prep-HPLC (Column: XBridge RP C18 OBD, 5  $\mu$ M, 19x50 mm; Mobile Phase A: Water/0.1% Formic Acid; Mobile Phase B: MeCN/0.1% Formic Acid; Flow rate: 23 mL/min; Gradient: 2% B to 50% B in 7 min) to afford the title compound (7.1 mg, 49% yield).  $^1H$ -NMR

## 210

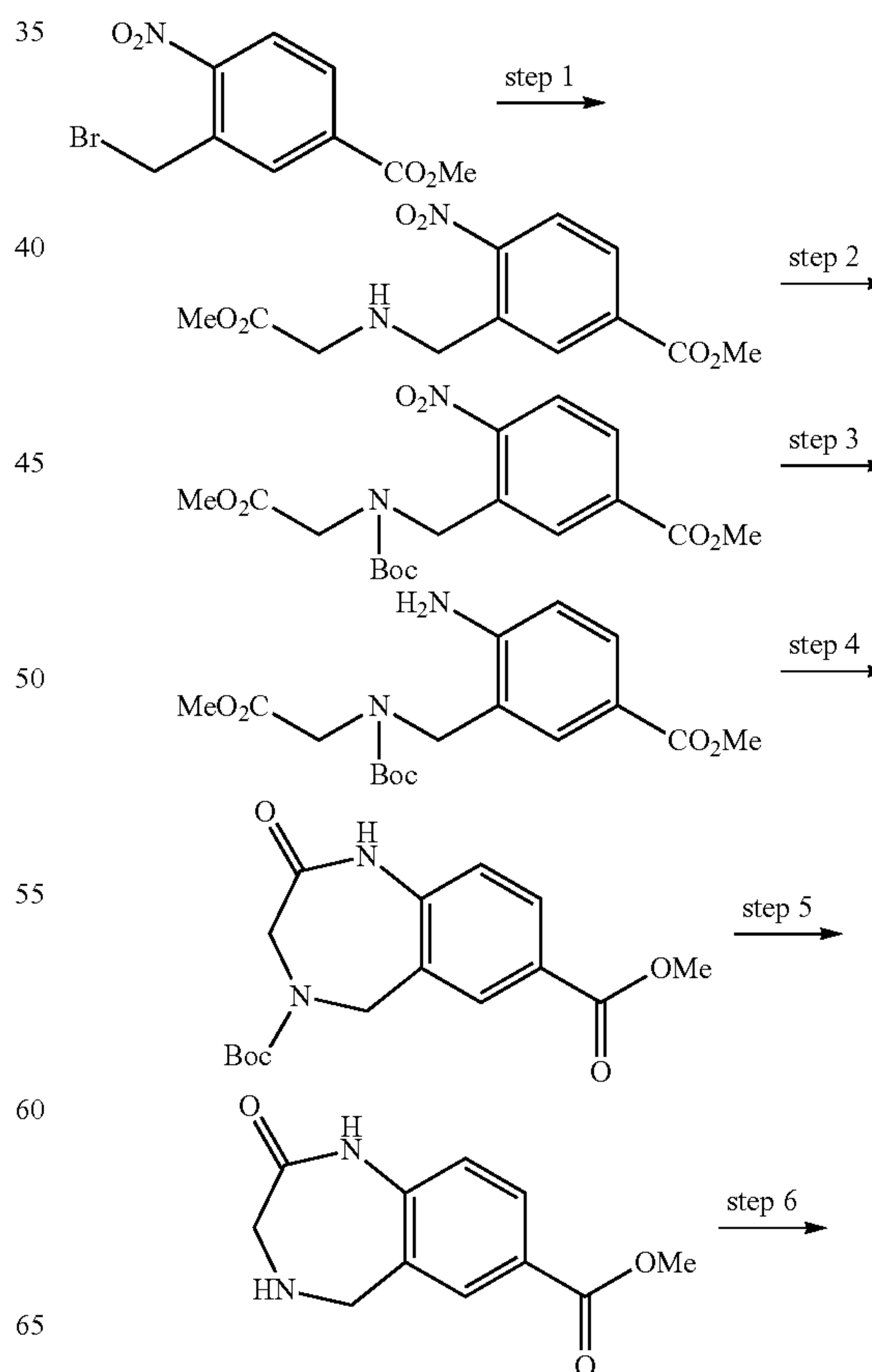
(300 MHz,  $DMSO-d_6$ )  $\delta$ (ppm): 11.19 (br s, 1H), 10.06 (s, 1H), 8.17 (s, 1H), 7.42 (s, 1H). 7.29-7.40 (m, 2H), 7.09 (d, J=8.5 Hz, 2H), 6.80 (d, J=8.5 Hz, 2H), 3.77-3.97 (m, 2H), 3.68 (s, 3 H), 3.27-3.33 (m, 2H), 2.65 (s, 4H). MS: (ES, m/z): 356  $[M+H]^+$ .

TABLE 33

The following compound was prepared according to the method of Example 69.	
Structure	Found M + H
	(ES, m/z): 356 $[M + H]^+$

## Example 70

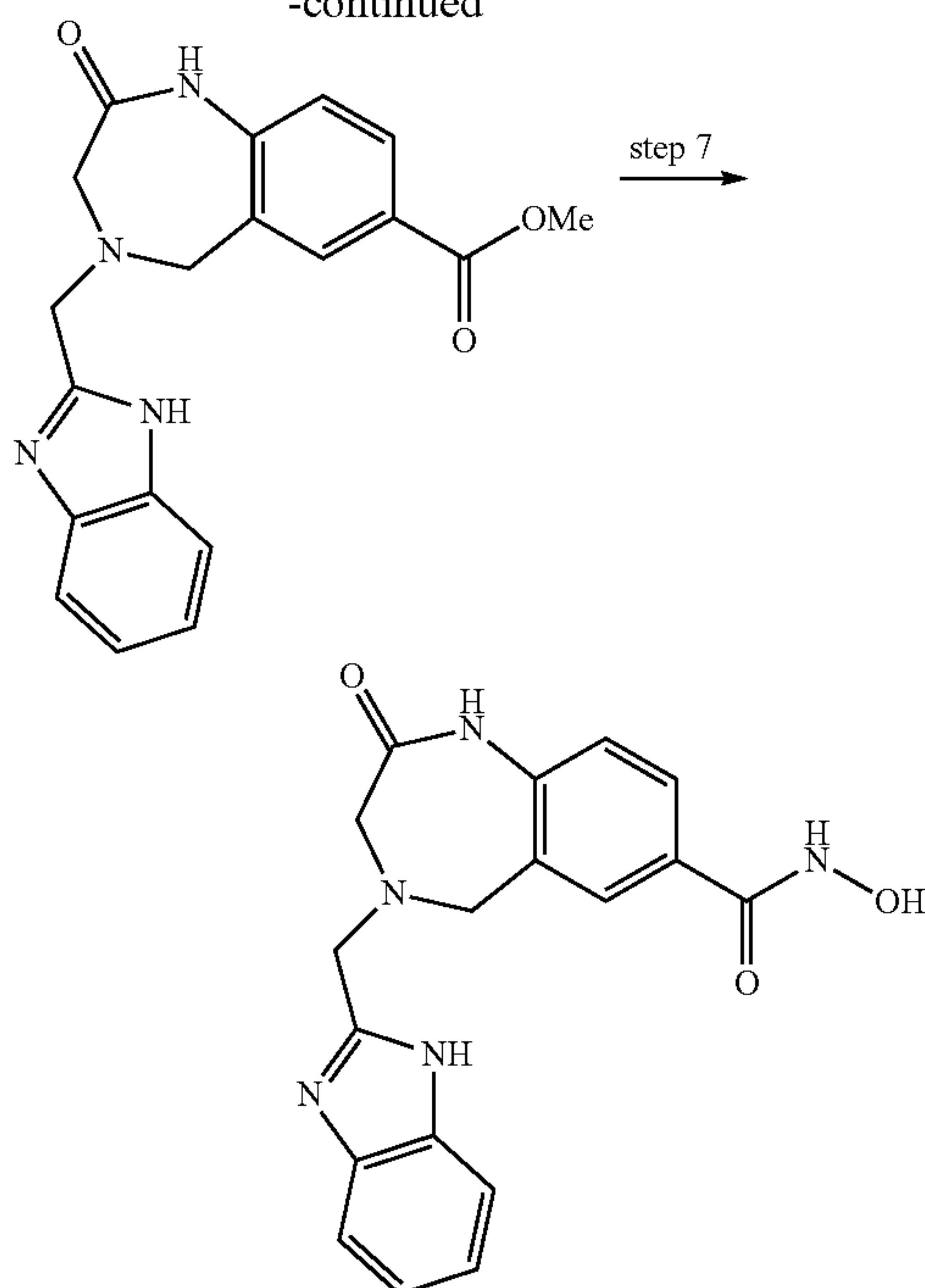
Preparation of 4-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide



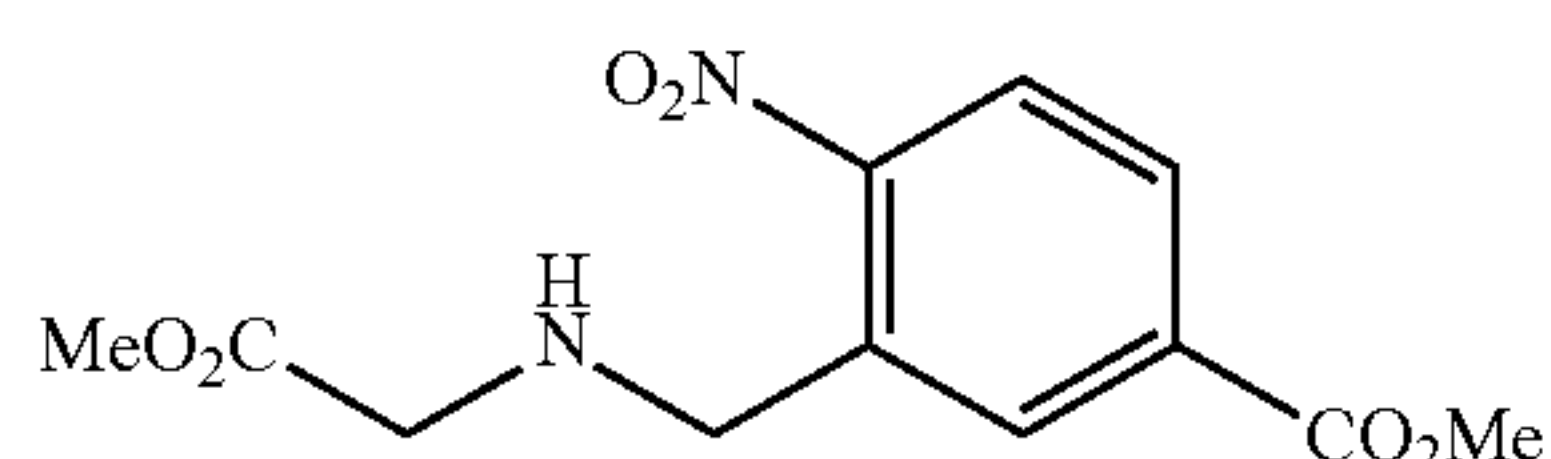


211

-continued

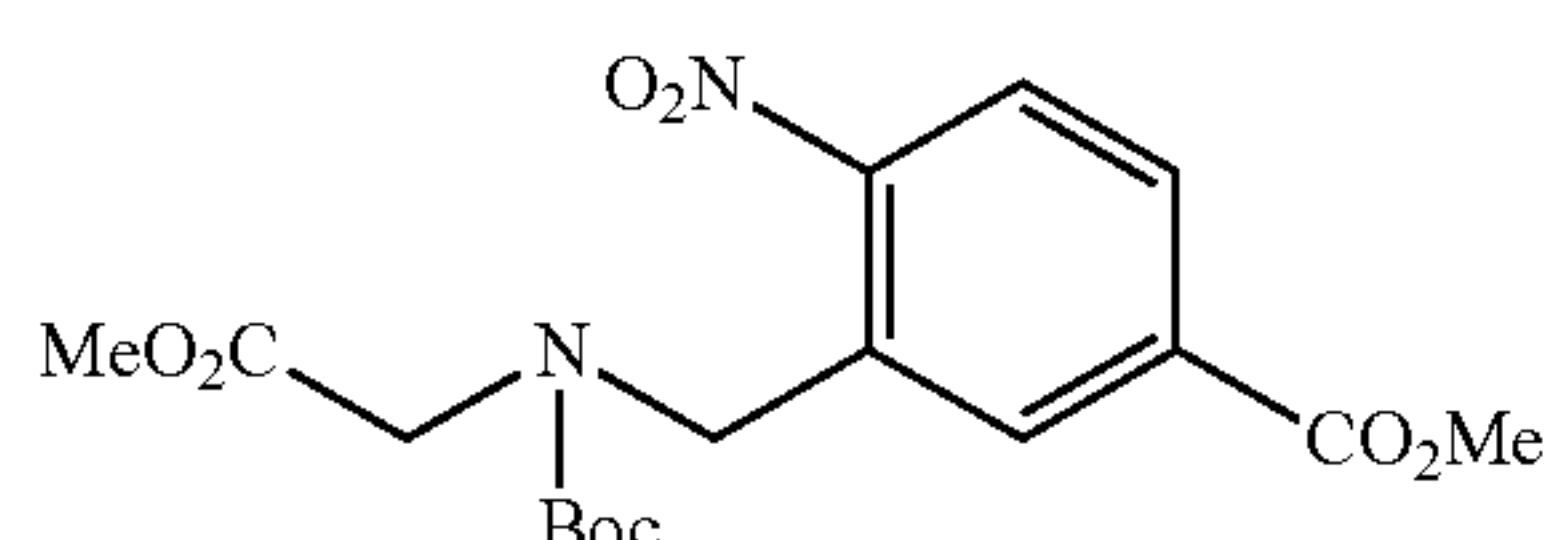


Step-1: Methyl 3-(((2-methoxy-2-oxoethyl)amino)methyl)-4-nitrobenzoate



Into a 250-mL round-bottom flask that has been purged and maintained with an inert atmosphere of nitrogen, were placed methyl 2-aminoacetate (12 g, 135 mmol, 1.5 equiv), methyl 3-(bromomethyl)-4-nitrobenzoate (12 g, 26 mmol, 1 equiv), DIEA (32 mL, 3 equiv) and DMF (120 mL). The resulting solution was stirred for 12 h at room temperature. The reaction was then quenched by the addition of water. The resulting solution was extracted with EtOAc (3×100 mL) and the combined organic layer was washed with brine (100 mL). The organic mixture was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (Gradient 1:10 to 1:1 EtOAc/hexanes) to afford the title compound as a yellow solid (4.9 g, 66% yield). MS: (ES, m/z): 283 [M+H]<sup>+</sup>.

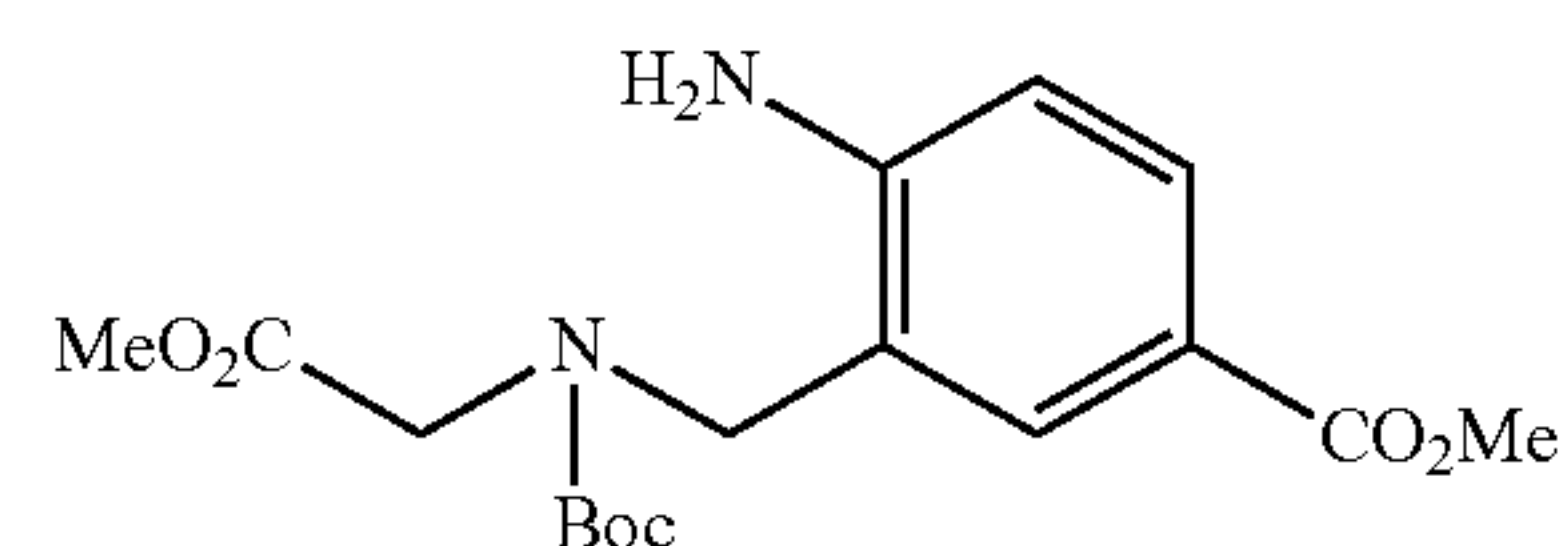
Step-2: Methyl 3-(((tert-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)methyl)-4-nitrobenzoate



212

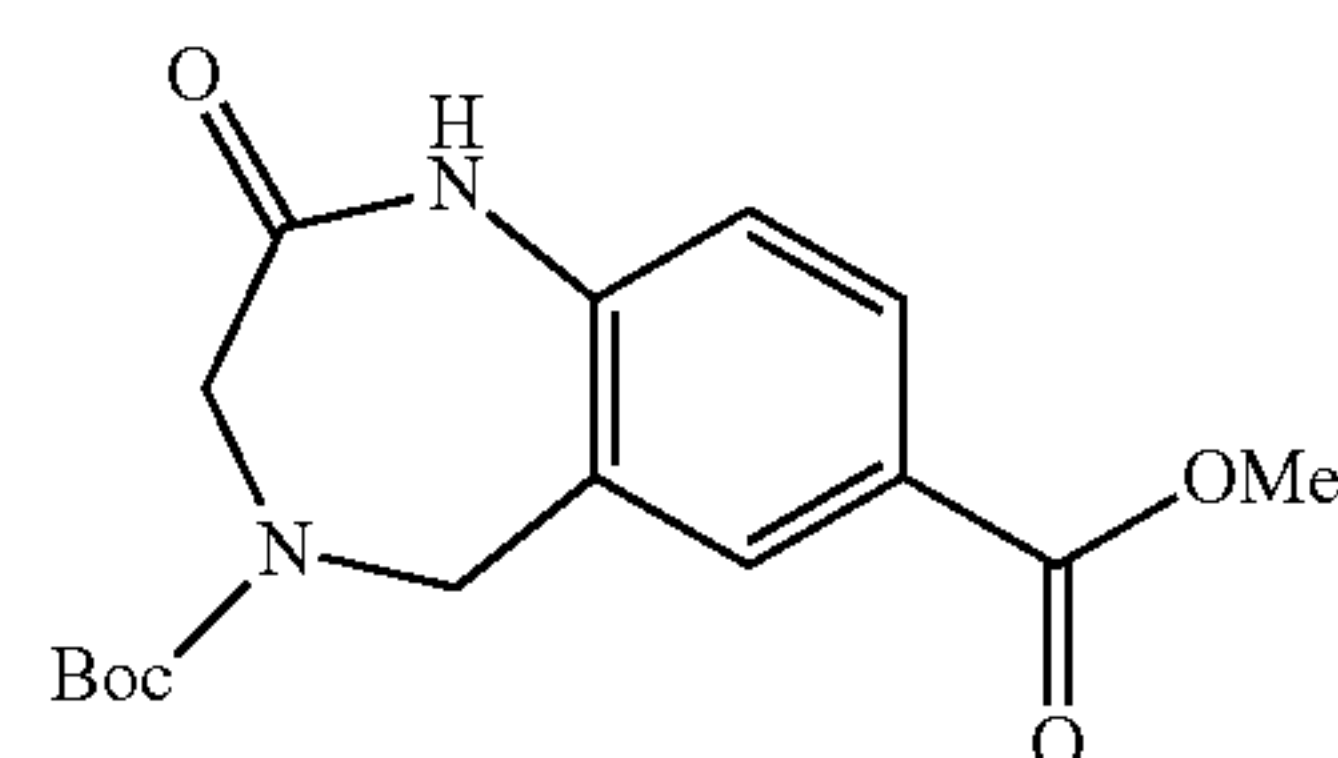
Into a 100-mL round-bottom flask, were placed methyl 3-(((2-methoxy-2-oxoethyl)amino)methyl)-4-nitrobenzoate (4.7 g, 16.8 mmol, 1 equiv), CH<sub>2</sub>Cl<sub>2</sub> (100 mL), di-tert-butyl dicarbonate (4.4 g, 20.2 mmol, 1.2 equiv) and 4-dimethylaminopyridine (82 mg, 0.67 mmol, 0.04 equiv). The resulting solution was stirred for 4 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (Gradient 1:10 to 1:1 EtOAc/petroleum ether) to afford the title compound as a yellow oil (2.8 g, 44% yield). MS: (ES, m/z): 283 [M-Boc+H]<sup>+</sup>.

Step-3: Methyl 4-amino-3-(((tert-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)methyl)benzoate



Into a 100-mL round-bottom flask, were placed methyl 3-(((tert-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)methyl)-4-nitrobenzoate (2.8 g, 7.3 mmol, 1 equiv), MeOH (30 mL) and palladium on carbon (280 mg). The resulting solution was stirred for 18 h at room temperature under a H<sub>2</sub> balloon. The solids were filtered out and the filtrate was concentrated under reduced pressure to afford the title compound as a brown oil (1.9 g, 74% yield). MS: (ES, m/z): 253 [M-Boc+H]<sup>+</sup>.

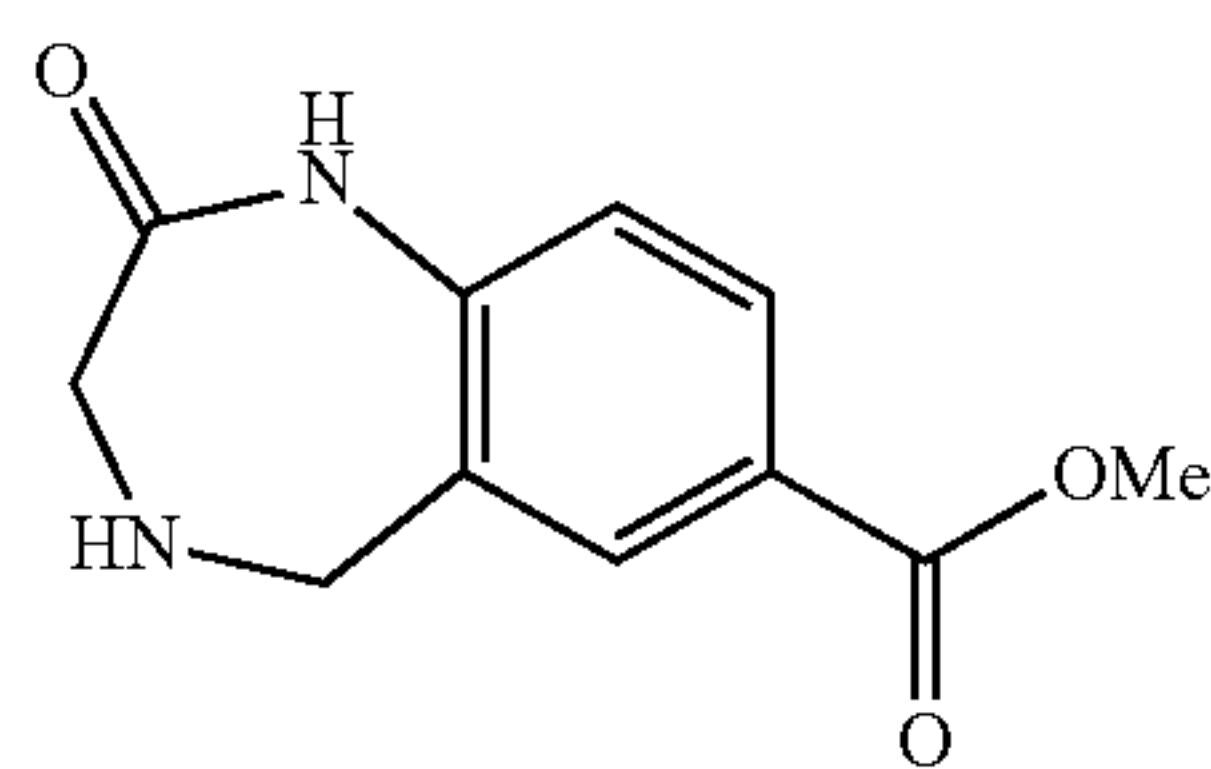
Step-4: 4-(tert-Butyl) 7-methyl 2-oxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4,7-dicarboxylate



Into a 250-mL round-bottom flask that has been purged and maintained with an inert atmosphere of nitrogen, were placed methyl 4-amino-3-(((tert-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)methyl)benzoate (1.9 g, 7.5 mmol, 1 equiv), THF (100 mL) and sodium hydride (239 mg, 10 mmol, 1.3 equiv). The resulting solution was stirred for 4 h at room temperature. The reaction mixture was poured into water/ice and extracted with EtOAc (3×150 mL). The combined organic layers was washed with brine (100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. The crude product was recrystallized from diethyl ether to afford the title compound as a white solid (0.5 g, 21% yield). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ(ppm): 10.34-10.41 (m, 1H), 7.76-7.79 (m, 2H), 7.17-7.20 (m, 1H), 4.27-4.53 (m, 4H), 3.82 (s, 3H), 1.34 (s, 3H), 1.20 (s, 6H).

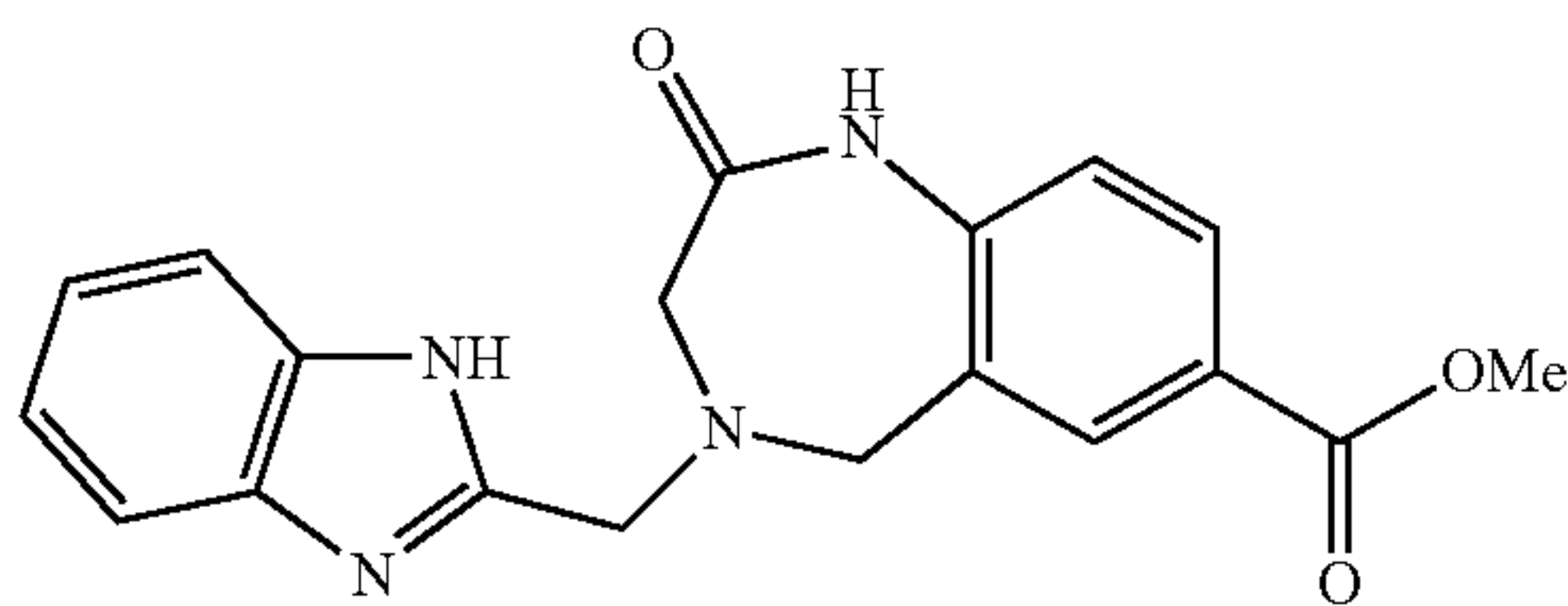
## 213

Step-5: Methyl 2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate



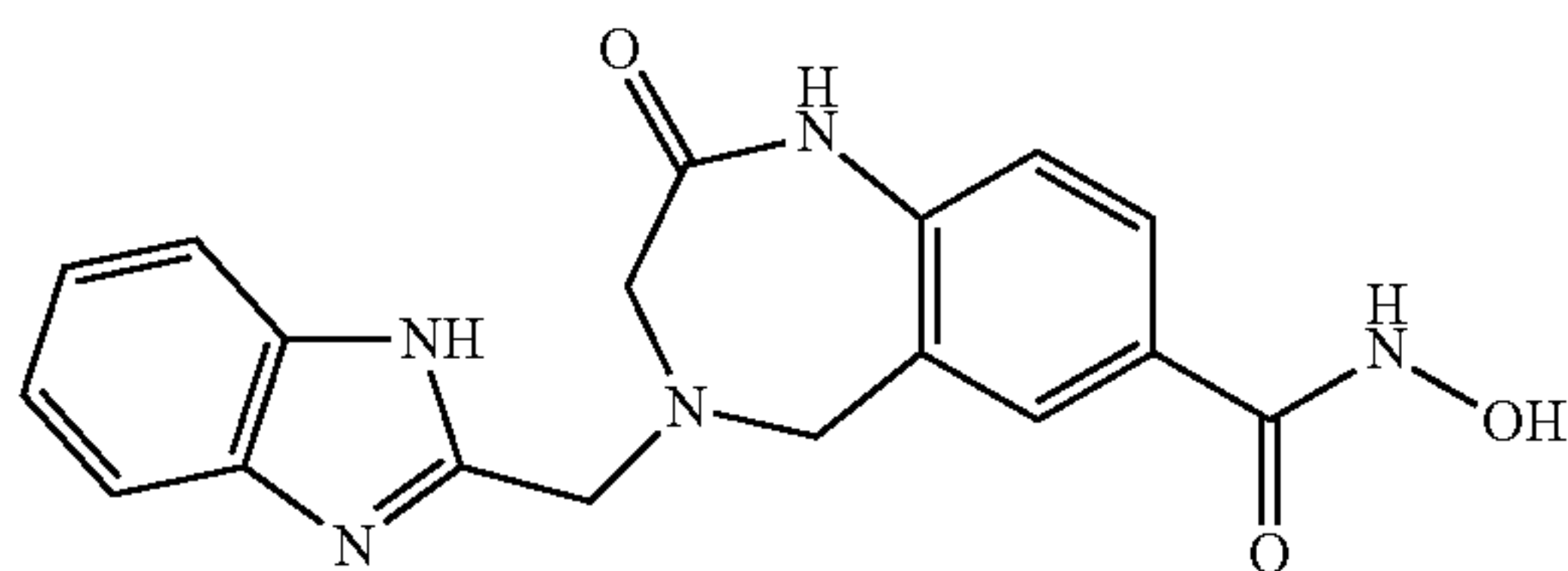
Into a 500-mL round-bottom flask that has been purged and maintained with an inert atmosphere of nitrogen, were placed 4-(tert-butyl) 7-methyl 2-oxo-1,2,3,5-tetrahydro-4H-benzo[e][1,4]diazepine-4,7-dicarboxylate (12 g, 37 mmol, 1 equiv) and 4N HCl in dioxane (360 mL). The resulting solution was stirred for 6 h at room temperature. The resulting mixture was concentrated under vacuum and washed with diethyl ether (300 mL) to afford the title compound as the HCl salt as a white solid (9.5 g, 99% yield). MS: (ES, m/z): 221 [M+H]<sup>+</sup>.

Step-6: Methyl 4-((1H-benzo[d]imidazol-2-yl)methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate



To a suspension of methyl 2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate hydrochloride (50 mg, 0.195 mmol, 1 equiv) and K<sub>2</sub>CO<sub>3</sub> (56.5 mg, 0.41 mmol, 2.1 equiv) in MeCN (1 mL) was added 2-(chloromethyl)-1H-benzo[d]imidazole (68 mg, 0.41 mmol, 2.1 equiv). The resulting mixture was heated at 55° C. for 2 days. The reaction mixture was partitioned between EtOAc and a saturated aqueous solution of NaHCO<sub>3</sub>. The layers were separated. The organic layer was washed with water, then with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was filtered, and concentrated. This crude material was purified by silica gel chromatography (Gradient 0-5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford the title compound as a yellow oil (54.5 mg, 80% yield). MS: (ES, m/z): 351 [M+H]<sup>+</sup>.

Step-7: 4-((1H-Benzo[d]imidazol-2-yl)methyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide



## 214

To a solution of methyl 4-((1H-benzo[d]imidazol-2-yl)methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (54 mg, 0.154 mmol, 1 equiv) in a MeOH/THF (4:1, 2 mL) were added NH<sub>2</sub>OH (50% in water, 996 μL, 16 mmol, 85 equiv) and aq. 2N NaOH solution (15 μL, 0.31 mmol, 2 equiv). The reaction was stirred at room temperature for 2 h, then was acidified with 2N HCl. The mixture was extracted with EtOAc and the separated organic layer was washed with brine, then dried over anhydrous MgSO<sub>4</sub>. The solution was filtered, and concentrated. This crude material was purified by Prep-HPLC (Column: XBridge RP C18 OBD, 5 μM, 19×50 mm; Mobile Phase A: Water/0.1% Formic Acid; Mobile Phase B: MeCN/0.1% Formic Acid; Flow rate: 23 mL/min; Gradient: 2% B to 50% B in 7 min) to afford the title compound (10.7 mg, 19% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 12.40 (br s, 1H), 11.12 (br s, 1H), 10.24 (s, 1H), 8.15 (s, 1H), 7.59-7.67 (m, 2H), 7.38-7.56 (m, 2H), 7.07-7.16 (m, 3H), 3.90 (s, 2H), 3.87 (s, 2H), 3.39 (s, 2H). MS: (ES, m/z): 352 [M+H]<sup>+</sup>.

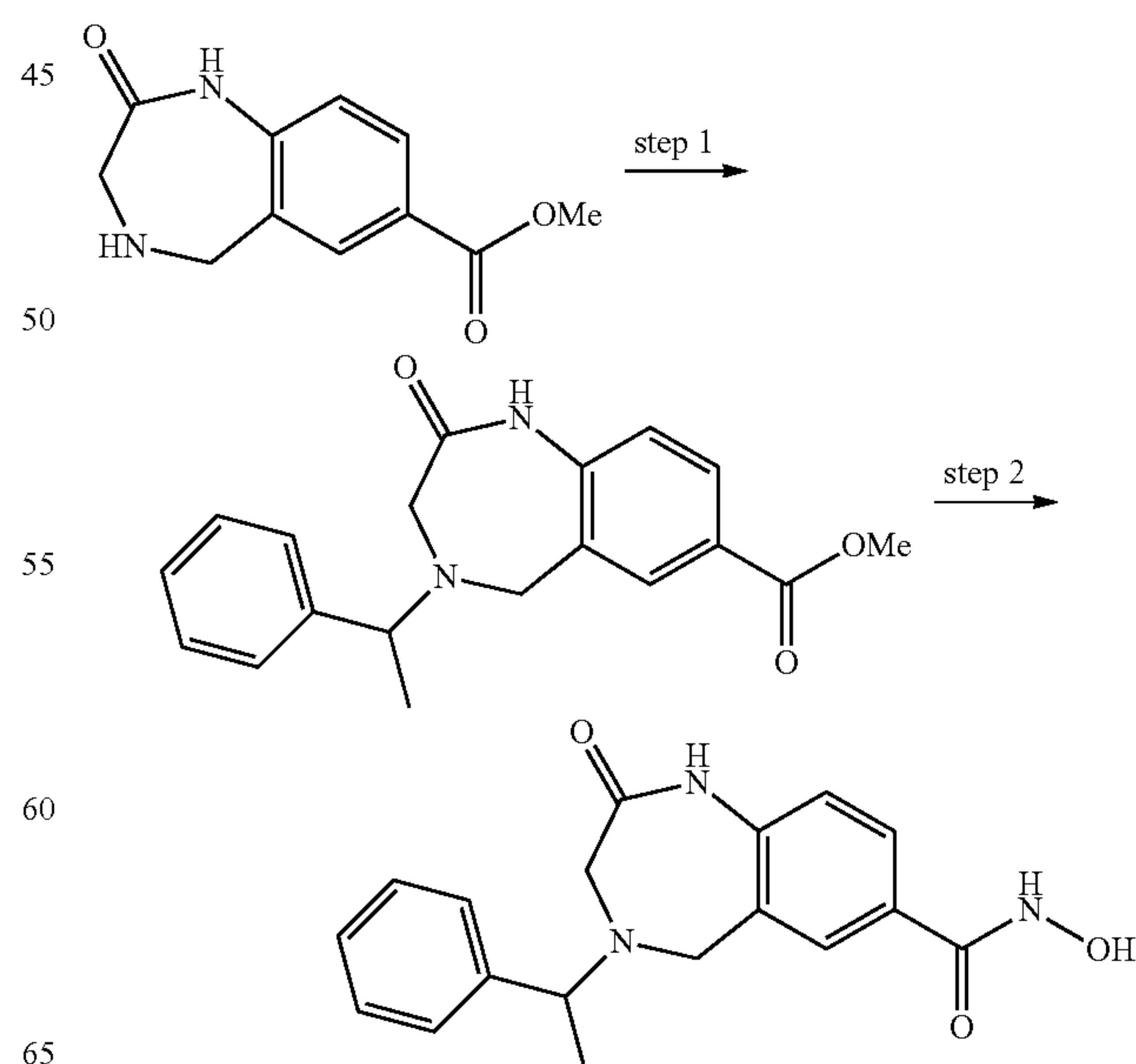
TABLE 34

The following compound was prepared according to the method of Example 70.

Structure	Found M + H
	(ES, m/z): 356 [M + H] <sup>+</sup>

Example 71

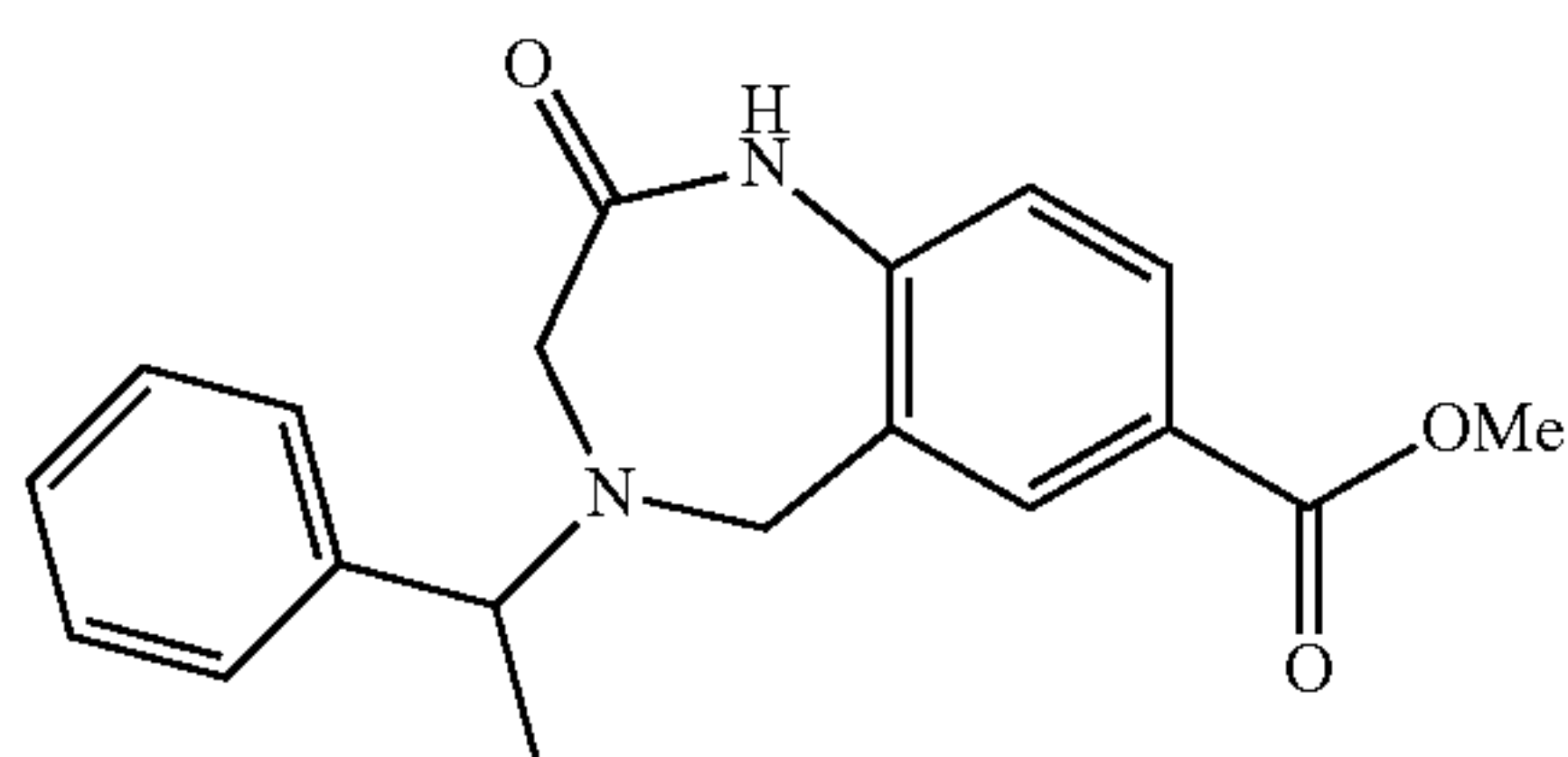
Preparation of N-hydroxy-2-oxo-4-(1-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide





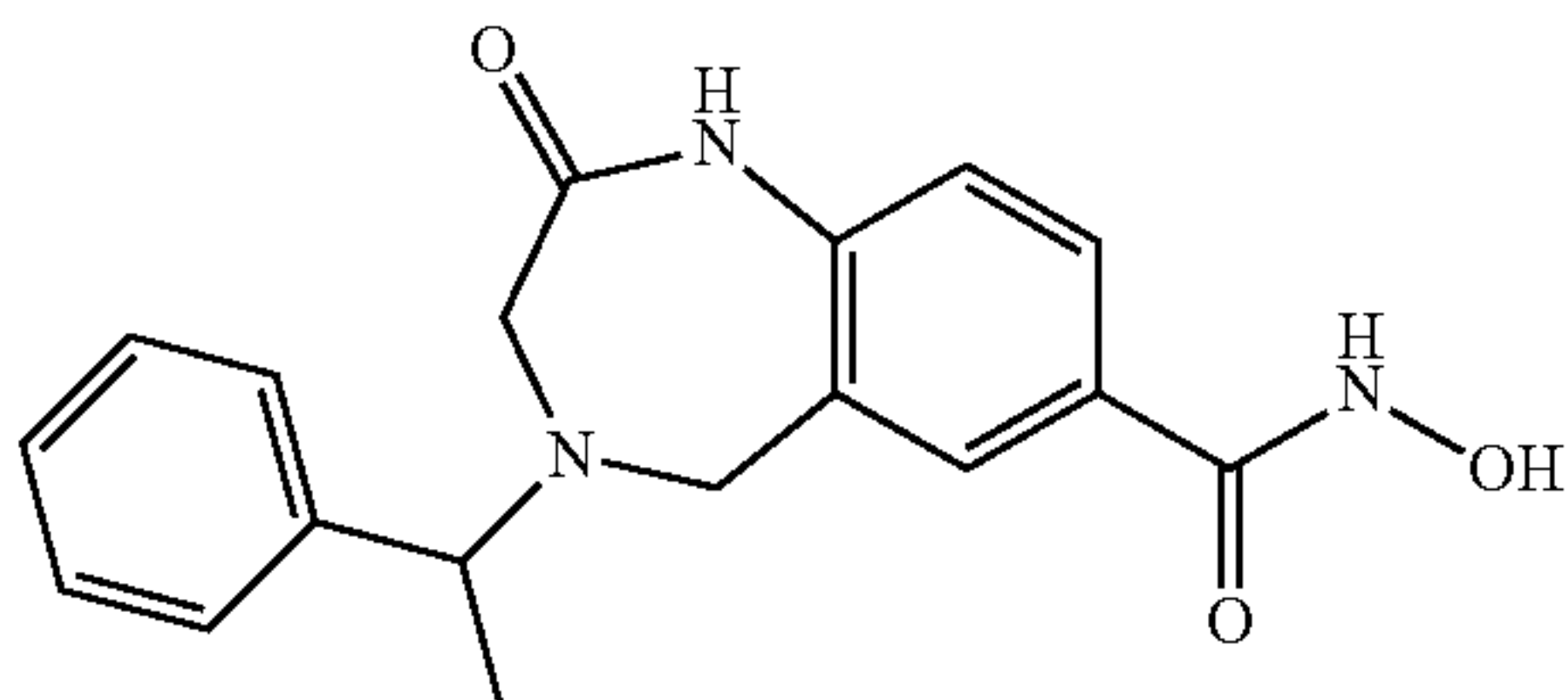
**215**

Step-1: Methyl 2-oxo-4-(1-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate



Into a 100-mL round-bottom flask, was placed methyl 2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxylate hydrochloride (100 mg, 0.39 mmol, 1 equiv), a solution of (1-bromoethyl)benzene (79 mg, 0.43 mmol, 1.1 equiv) in MeCN (5 mL) and DIEA (252 mg, 1.95 mmol, 5 equiv). The resulting solution was stirred overnight at 50° C. in an oil bath. The resulting mixture was concentrated under vacuum, diluted with H<sub>2</sub>O (30 mL), and extracted with EtOAc (3×100 mL). The combined organic layers were concentrated and purified by silica gel chromatography (EtOAc/pet. ether, 1:1) to afford the title compound as a yellow solid (110 mg, 87% yield).

Step-2: N-Hydroxy-2-oxo-4-(1-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide

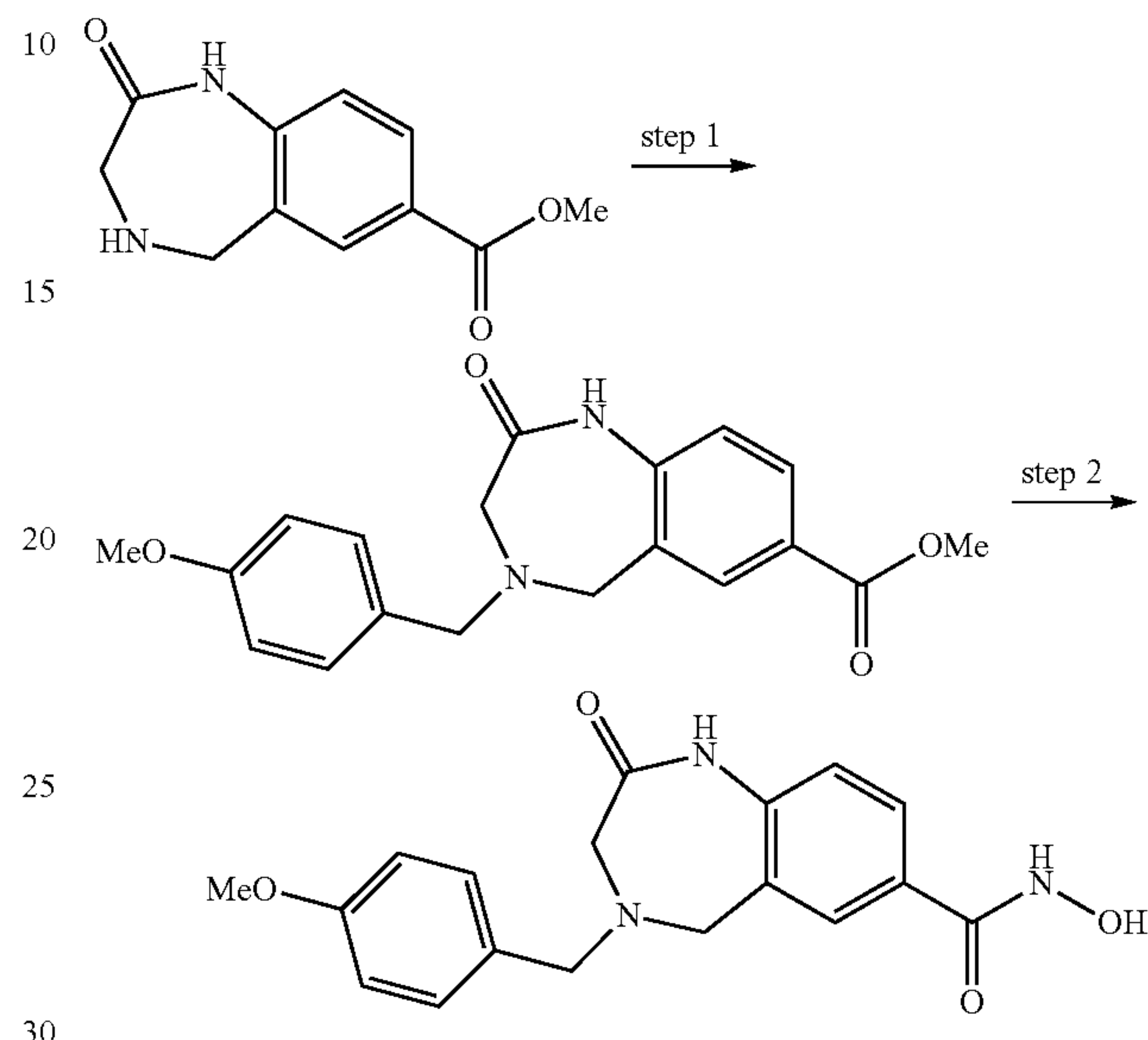


Into a 100-mL round-bottom flask, was placed a solution of methyl 2-oxo-4-(1-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (110 mg, 0.34 mmol, 1 equiv) in THF/MeOH (2.5 mL, 4:1), NH<sub>2</sub>OH (50% in water, 1 mL, 60 equiv), aq. 1N NaOH (0.5 mL, 2 equiv). The resulting solution was stirred for 6 h at room temperature. The crude product was purified by Prep-HPLC (Column: Xbridge RP C18 OBD, 5 μm, 19×50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: MeCN/0.05% TFA; Flow rate: 30 mL/min; Gradient: 10% B to 53% B in 8 min; Detector, UV 254, 220 nm) to afford the title compound as a light yellow solid (19 mg, 16% yield). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ(ppm): 11.22 (s, 1H), 10.60 (s, 1H), 7.77-7.75 (d, J=6.9 Hz, 2H), 7.45-7.41 (m, 5H), 7.16-7.13 (d, J=8.4 Hz, 1H), 4.16 (s, 3H) 3.52-3.44 (m, 2H), 1.55 (s, 3H). MS: (ES, m/z): 326 [M+H]<sup>+</sup>.

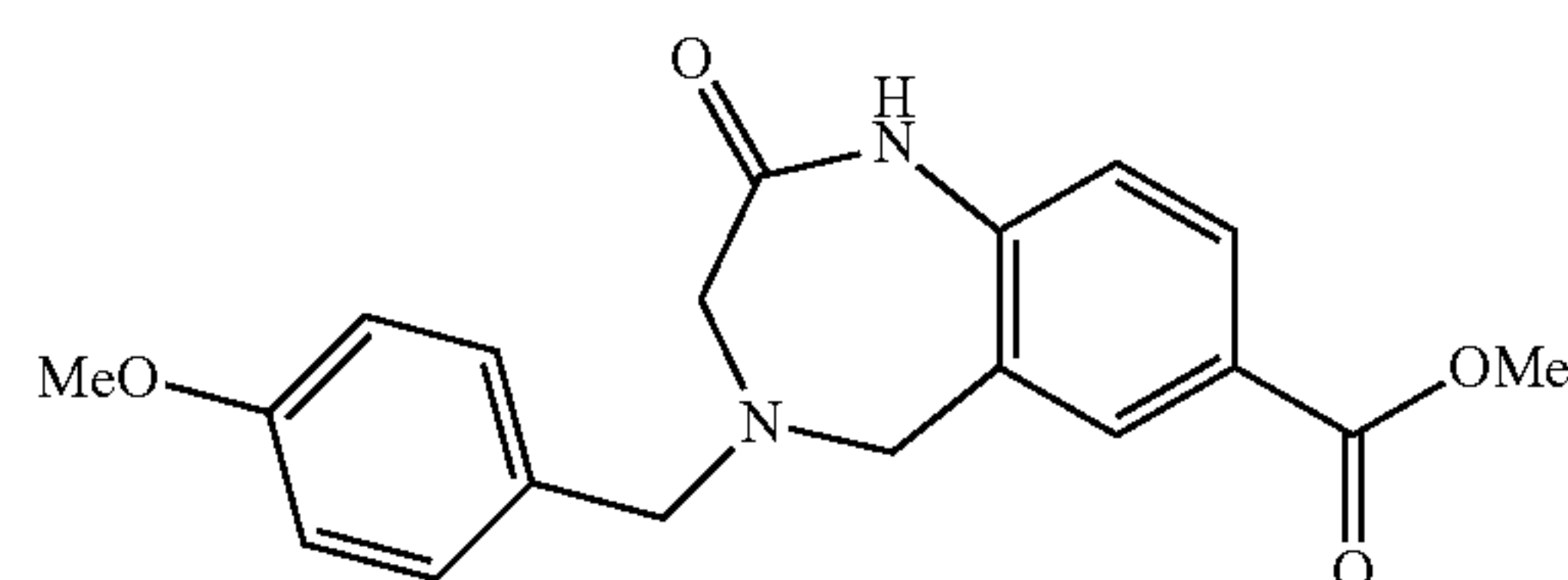
**216**

Example 72

Preparation of N-Hydroxy-4-(4-methoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide



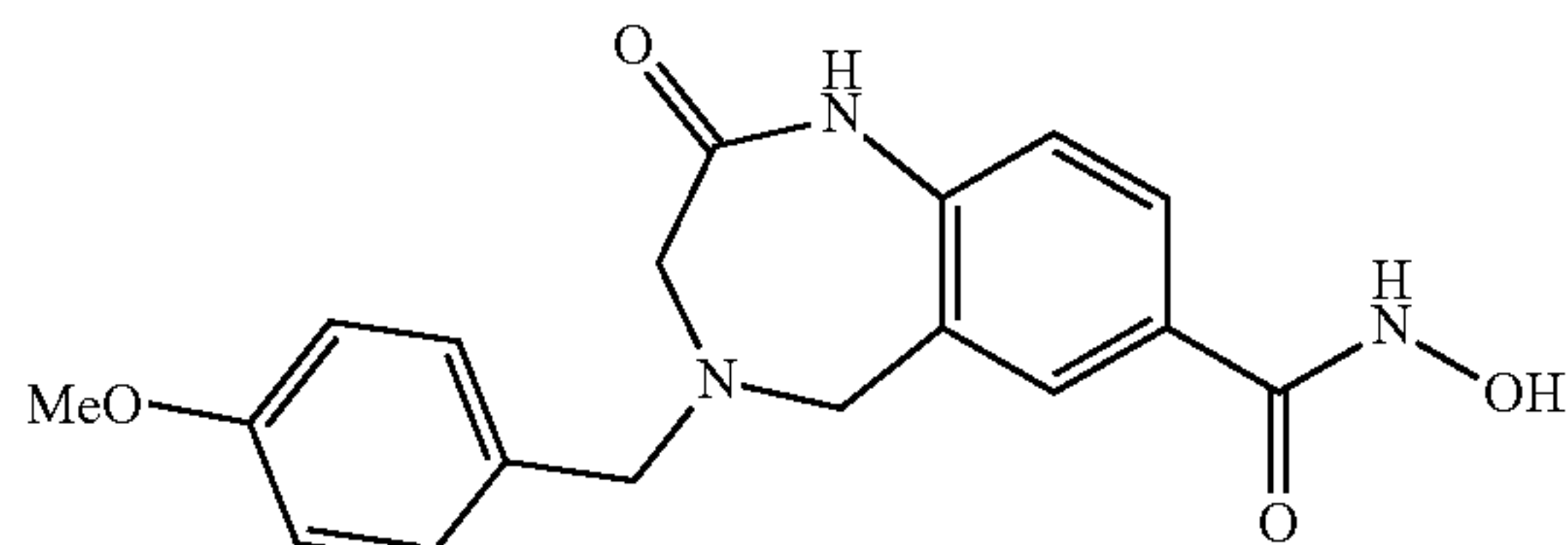
Step-1: Methyl 4-(4-methoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate



To a suspension of methyl 2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate hydrochloride (45 mg, 0.175 mmol, 1 equiv) in 1,2-dichloroethane (1.8 mL) were added p-anisaldehyde (32 μL, 0.263 mmol, 1.5 equiv) and Et<sub>3</sub>N (24 μL, 0.175 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (93 mg, 0.438 mmol, 2.5 equiv) was added to the reaction mixture and stirred at room temperature overnight. LCMS showed reaction completed. The reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and a saturated aqueous solution of NaHCO<sub>3</sub>. The layers were separated. The organic layer was washed with brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was filtered, and concentrated. This crude material was purified by silica gel chromatography (Gradient 10-100% EtOAc/hexanes) to afford the title compound as a white solid (47.8 mg, 80% yield). MS: (ES, m/z): 341 [M+H]<sup>+</sup>.

**217**

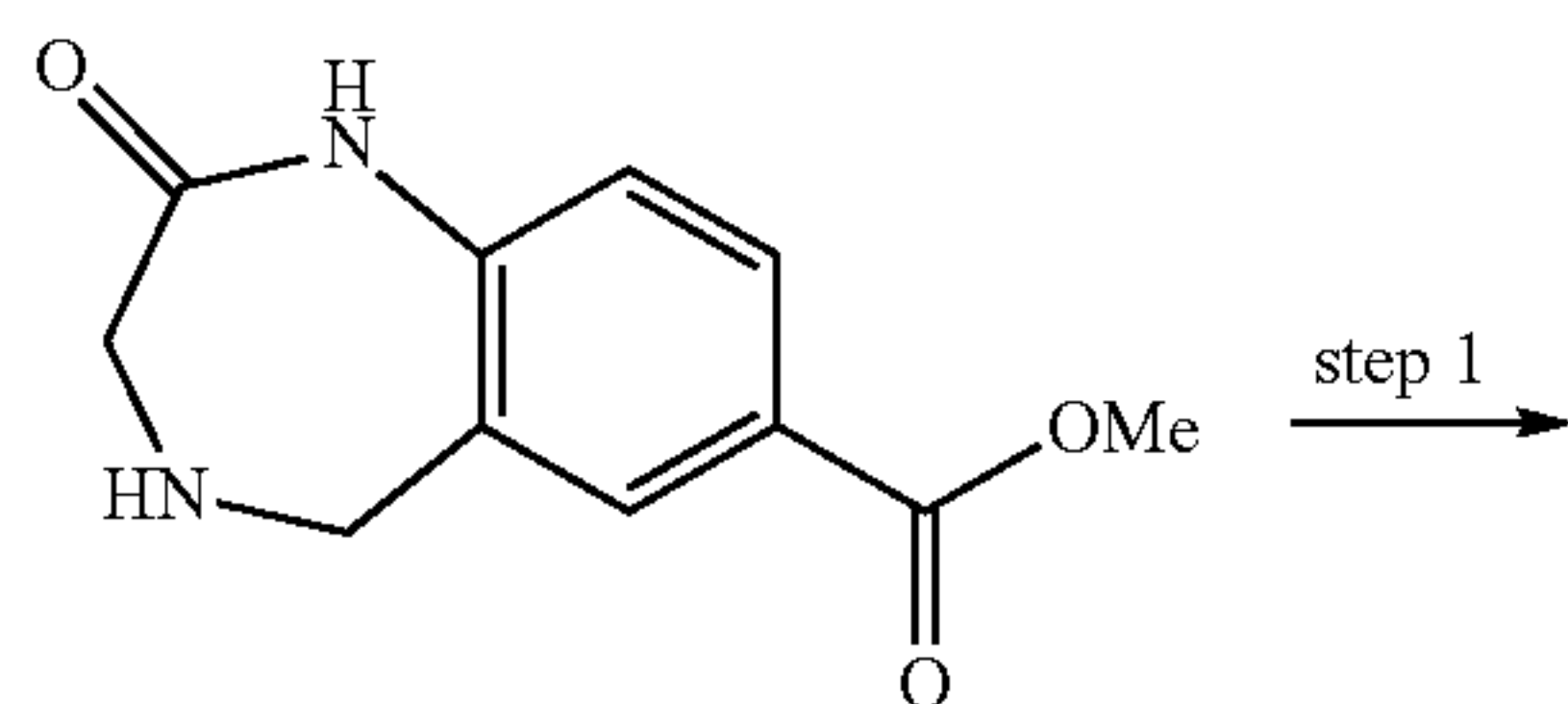
Step-2: N-Hydroxy-4-(4-methoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide



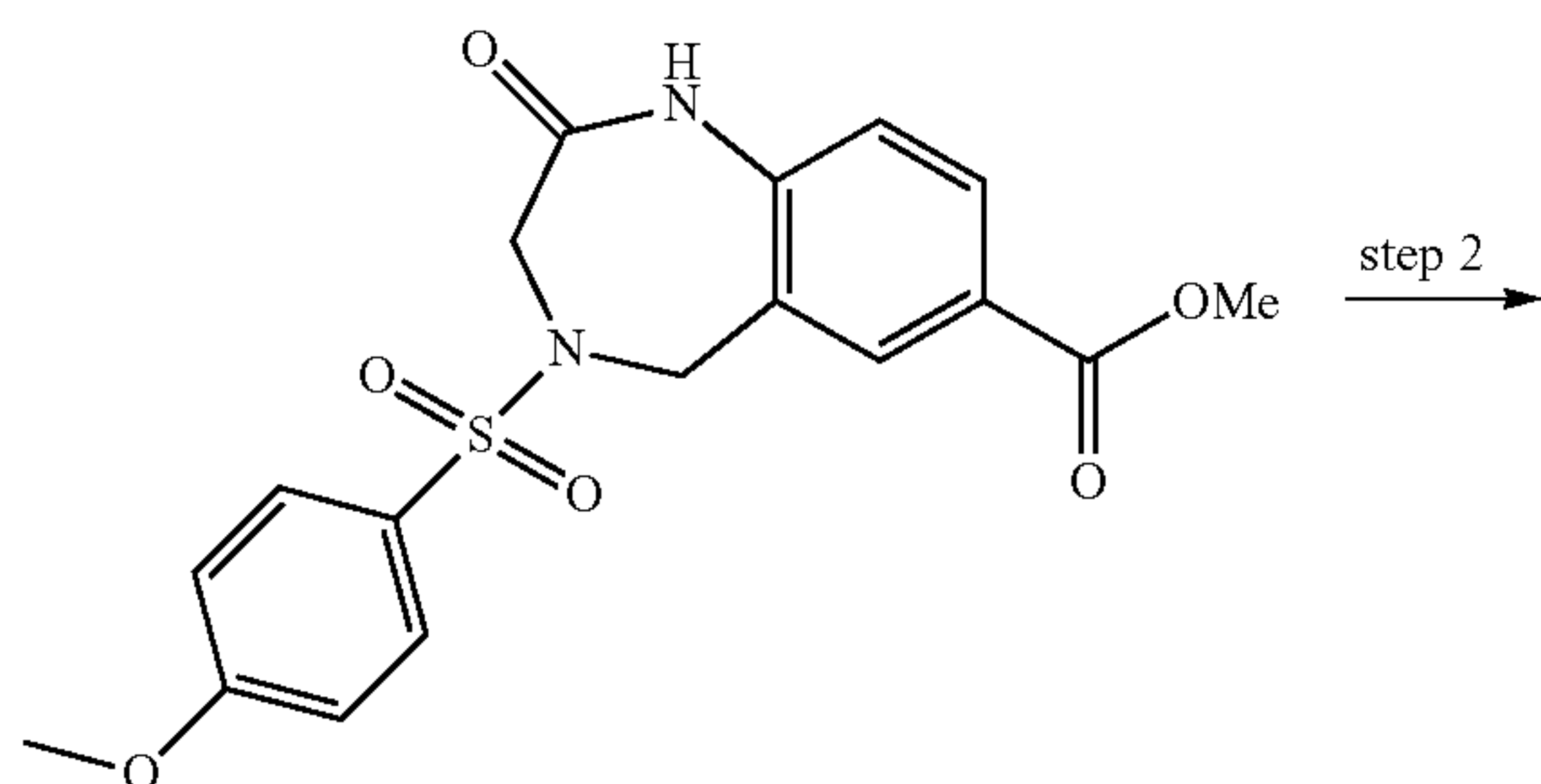
To a solution of methyl 4-(4-methoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (47 mg, 0.138 mmol, 1 equiv) in a MeOH/THF (1.4 mL, 1/4) were added an aqueous 50% wt hydroxylamine solution (169  $\mu$ L, 2.76 mmol, 20 equiv) and aqueous 2N NaOH solution (138  $\mu$ L, 0.276 mmol, 2 equiv). The reaction was stirred at room temperature for 2 days, then was acidified with 2N HCl. The mixture was concentrated and the residue was purified by Prep-HPLC (Column: Xbridge RP C18 OBD, 5  $\mu$ m, 19 $\times$ 50 mm; Mobile Phase A: Water/0.1% Formic Acid; Mobile Phase B: MeCN/0.1% Formic Acid; Flow rate: 23 mL/min; Gradient: 5% B to 50% B in 7 min) to afford the title compound as a yellow oil (23 mg, 49% yield).  $^1$ H-NMR (300 MHz, DMSO- $d_6$ )  $\delta$ (ppm): 11.10 (br s, 1H), 10.18 (s, 1H), 8.11 (s, 1H), 7.57-7.66 (m, 1H), 7.53 (s, 1H), 7.14-7.21 (m, 2H), 7.06 (d, J=8.5 Hz, 1H), 6.86 (br d, J=8.5 Hz, 2H), 3.65-3.75 (m, 5H), 3.56 (s, 2H), 3.22 (s, 2H). MS: (ES, m/z): 342 [M+H] $^+$ .

**Example 73**

Preparation of N-Hydroxy-4-((4-methoxyphenyl)sulfonyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide



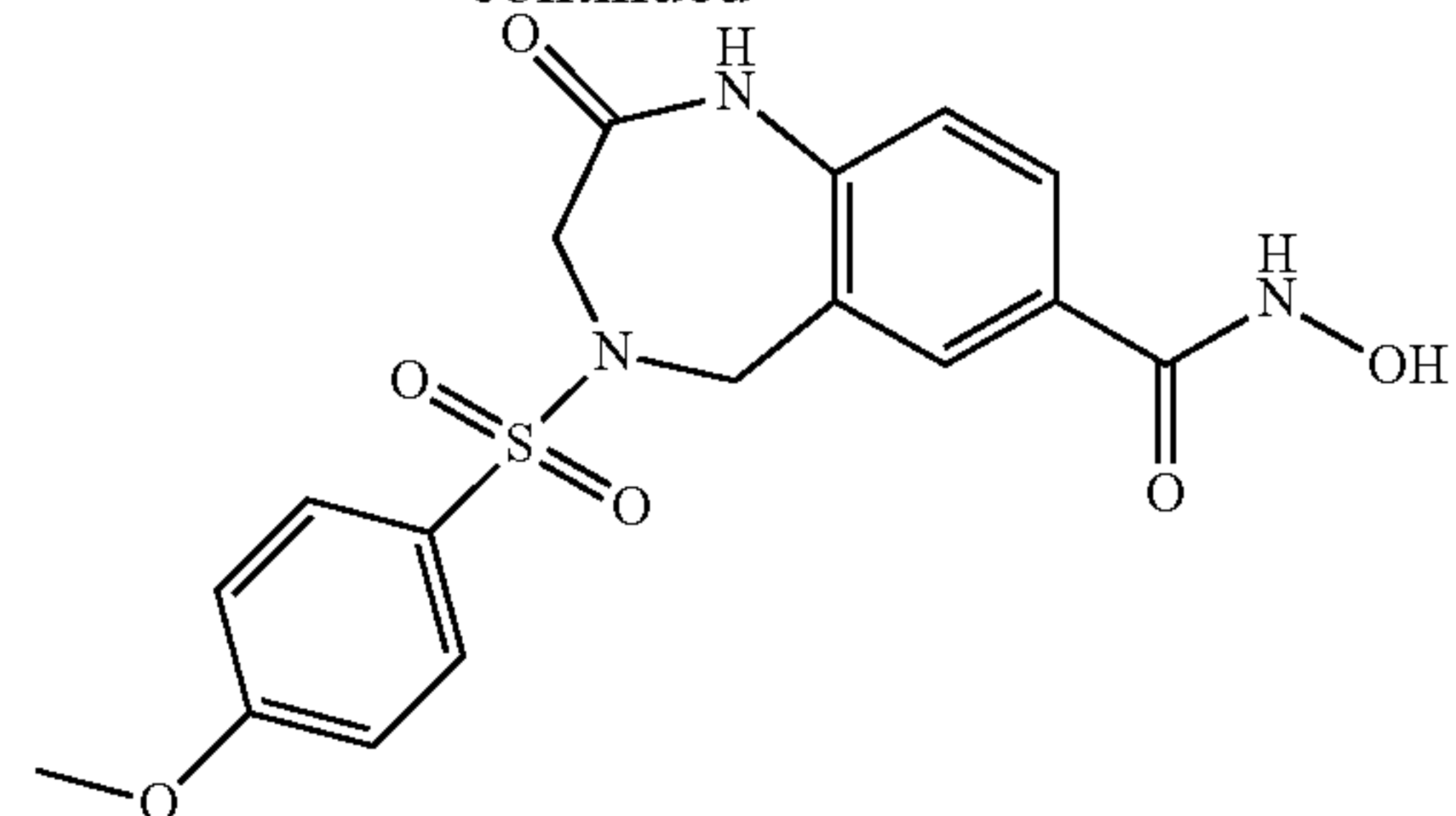
step 1



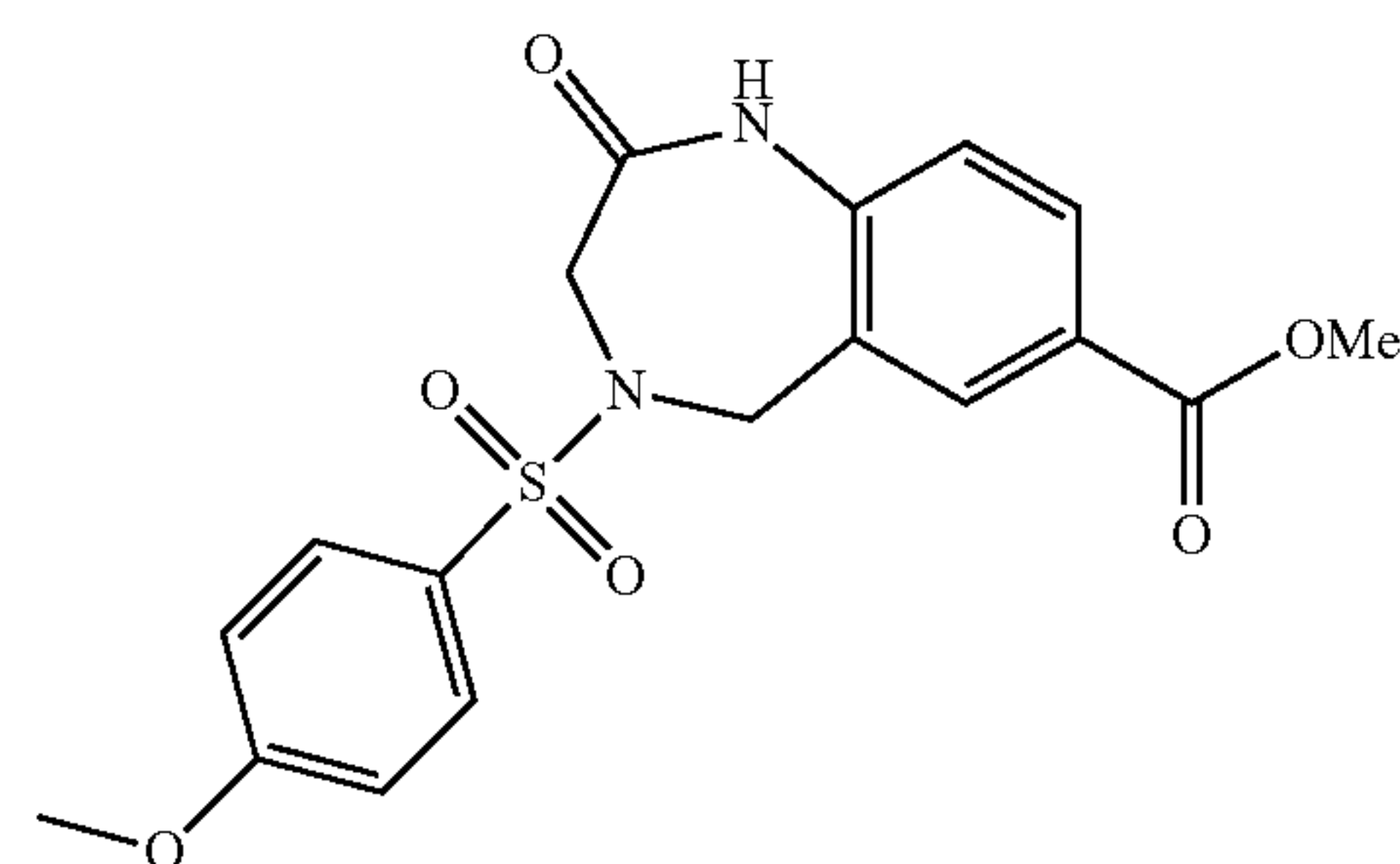
step 2

**218**

-continued

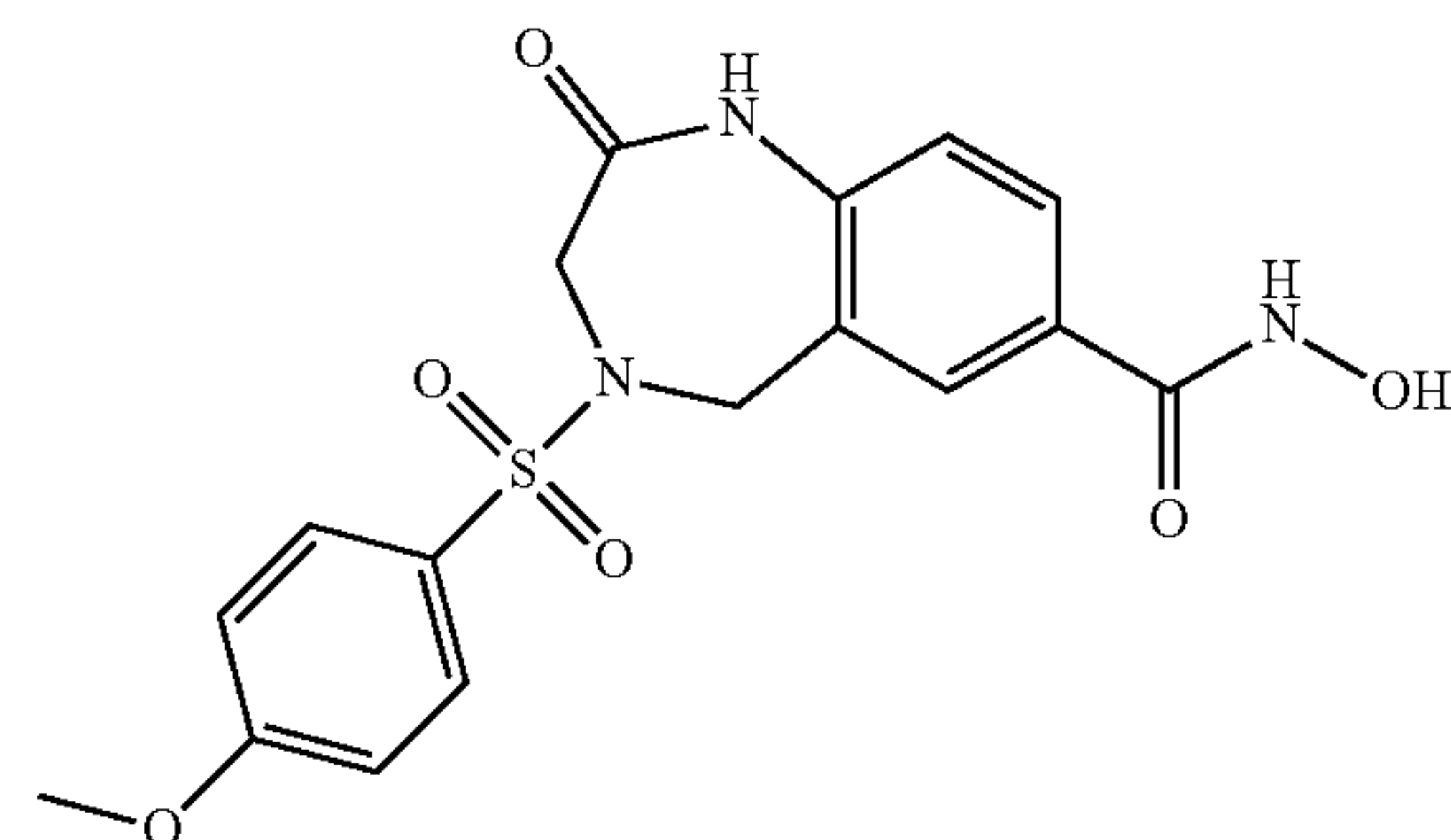


Step-1: Methyl 4-((4-methoxyphenyl)sulfonyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate



To a suspension of methyl 2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate hydrochloride (35 mg, 0.136 mmol, 1 equiv) in THF (1.4 mL) were added DIEA (83  $\mu$ L, 0.477 mmol, 3.5 equiv) and 4-methoxybenzene-1-sulfonyl chloride (34 mg, 0.164 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between EtOAc and a saturated aqueous solution of NaHCO<sub>3</sub>. The layers were separated. The organic layer was washed with brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was filtered, and concentrated to afford the title compound as a white solid (52.7 mg) which was used without further purification. MS: (ES, m/z): 391 [M+H] $^+$ .

Step-2: N-Hydroxy-4-((4-methoxyphenyl)sulfonyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide



To a solution of methyl 4-((4-methoxyphenyl)sulfonyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (49.4 mg, 0.127 mmol, 1 equiv) in a MeOH/THF

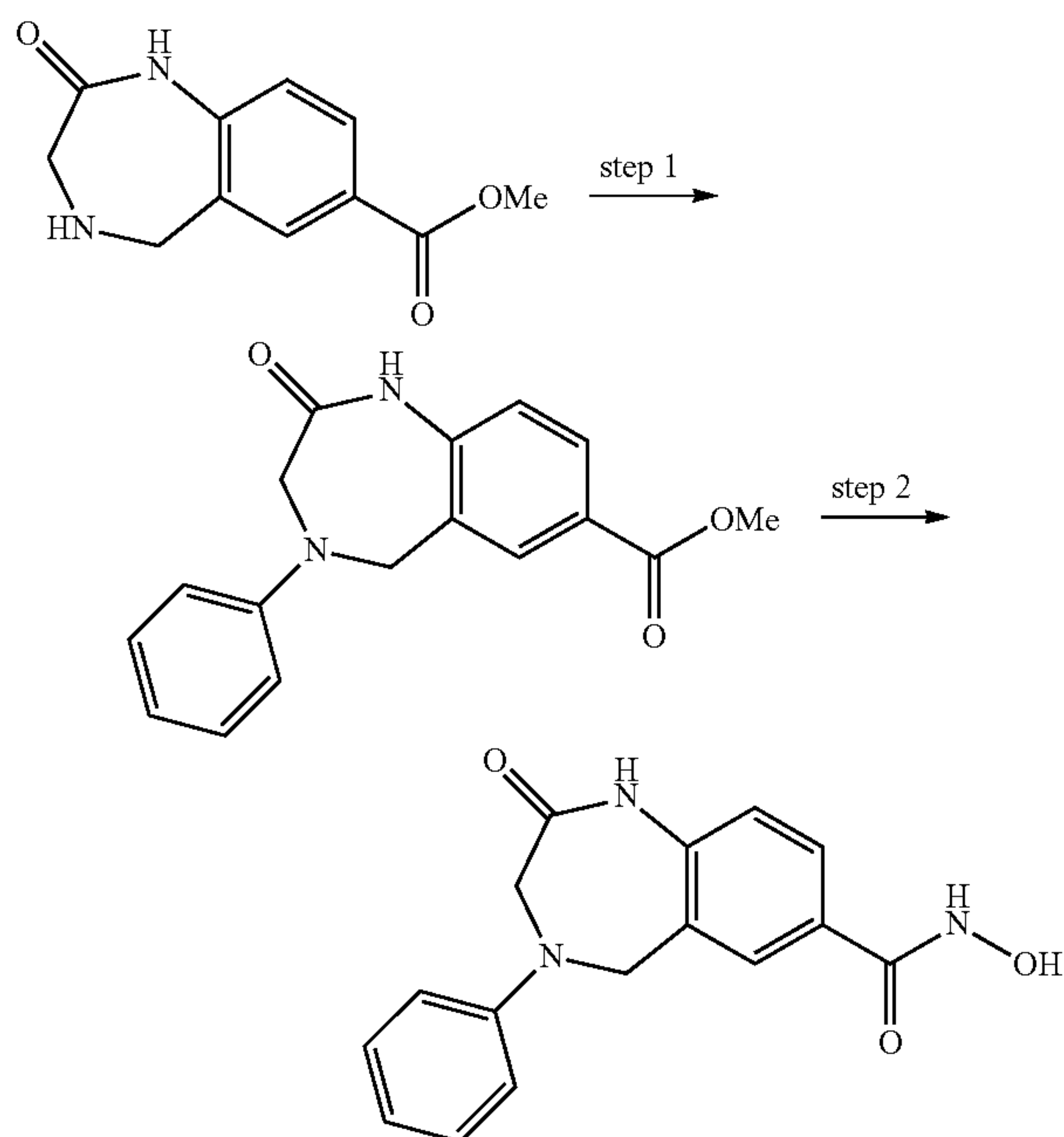


## 219

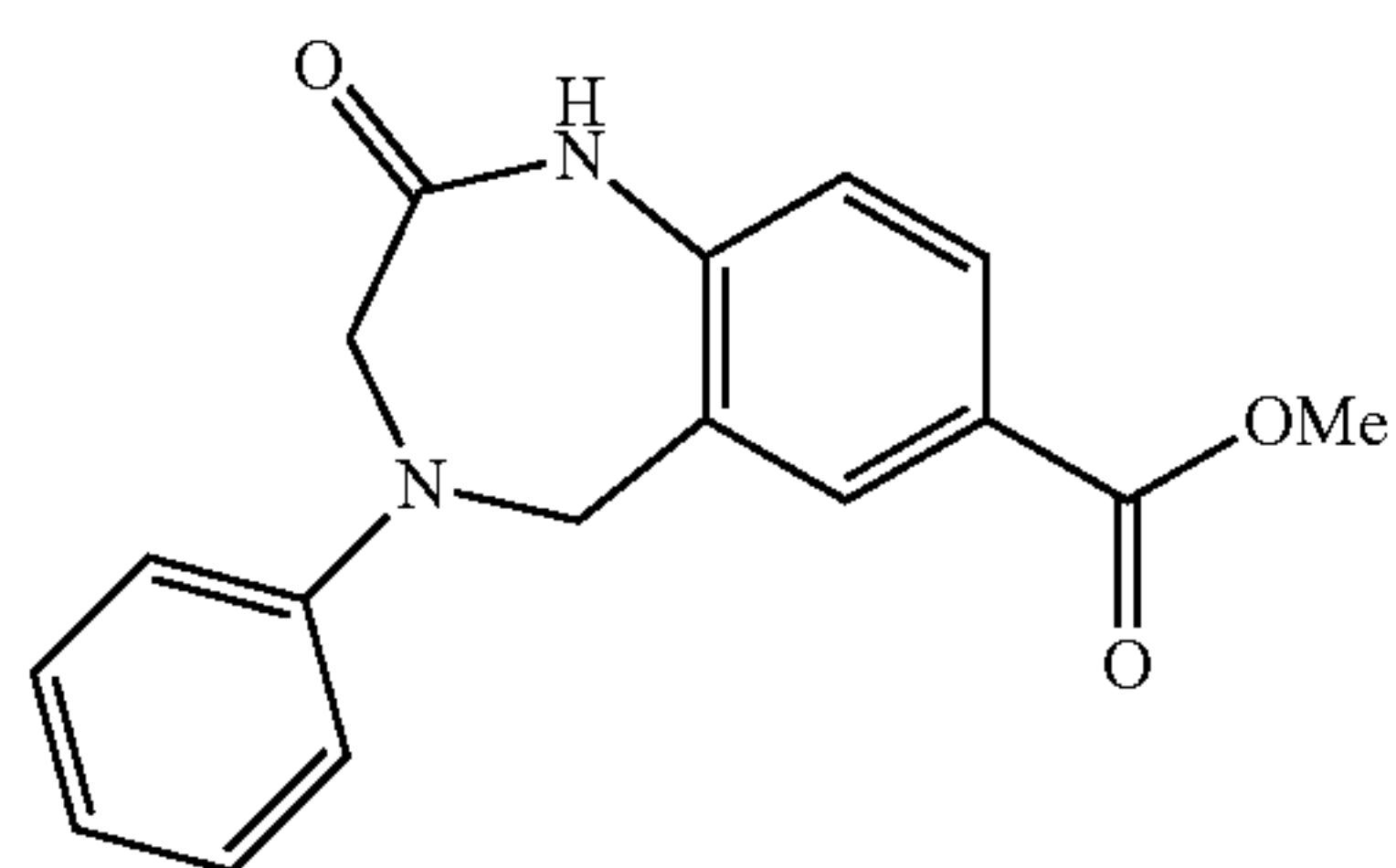
(1.3 mL, 1:4) were added  $\text{NH}_2\text{OH}$  (50% in water, 155  $\mu\text{L}$ , 2.53 mmol, 20 equiv) and aq. 2N NaOH solution (127  $\mu\text{L}$ , 0.253 mmol, 2 equiv). The reaction was stirred at room temperature for 2 days. The reaction was acidified to pH 6 with 2N HCl and the solution was directly purified by Prep-HPLC (Column: Xbridge RP C18 OBD, 5  $\mu\text{m}$ , 19 $\times$ 50 mm; Mobile Phase A: Water/0.1% Formic Acid; Mobile Phase B: MeCN/0.1% Formic Acid; Flow rate: 20 mL/min; Gradient: 5% B to 70% B in 7 min) to afford the title compound as a white solid (6.3 mg, 13% yield).  $^1\text{H-NMR}$  (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 11.12 (br s, 1H), 10.17 (s, 1H), 9.01 (br s, 1 H), 7.48-7.64 (m, 4 H), 6.79-7 (m, 3 H), 4.45 (s, 2H), 4.06 (s, 2 H), 3.77 (s, 3 H). MS: (ES,  $m/z$ ): 392  $[\text{M}+\text{H}]^+$ .

## Example 74

Preparation of N-Hydroxy-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide



Step-1: Methyl 2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate

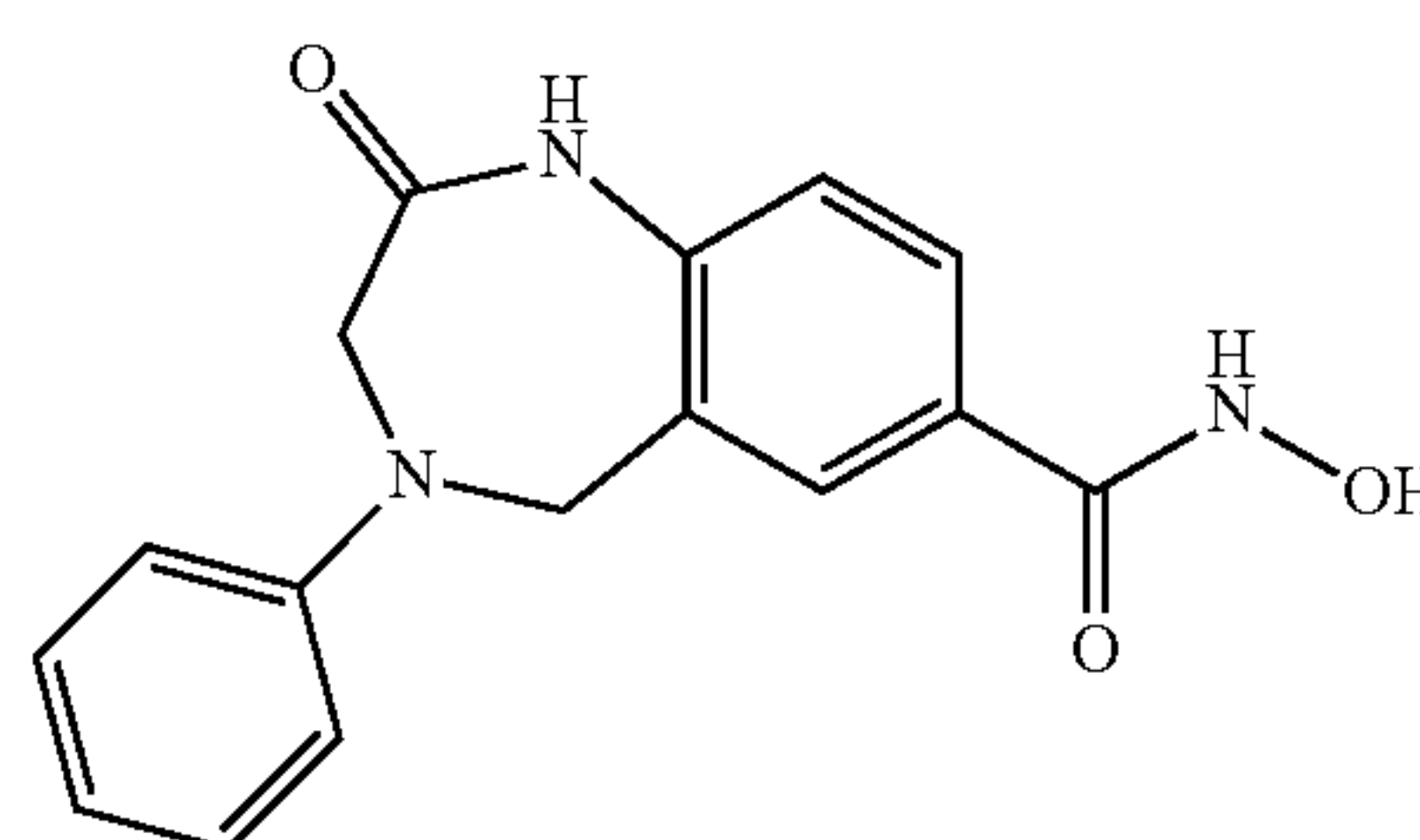


A mixture of methyl 2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (60 mg, 0.234 mmol, 1 equiv), bromobenzene (0.025 mL, 0.234 mmol, 1 equiv),

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sodium tert-butoxide (29.2 mg, 0.304 mmol, 1.3 equiv) and XPhos-Pd-G3 (10 mg, 0.012 mmol, 0.05 equiv) in 1,4-dioxane (2 mL) was heated at 80° C. overnight. The reaction was partitioned between water and  $\text{CH}_2\text{Cl}_2$ . The separated aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined organic layers were concentrated to afford the title compound as a pale yellow solid (11.9 mg, 17% yield). MS: (ES,  $m/z$ ): 297  $[\text{M}+\text{H}]^+$ .

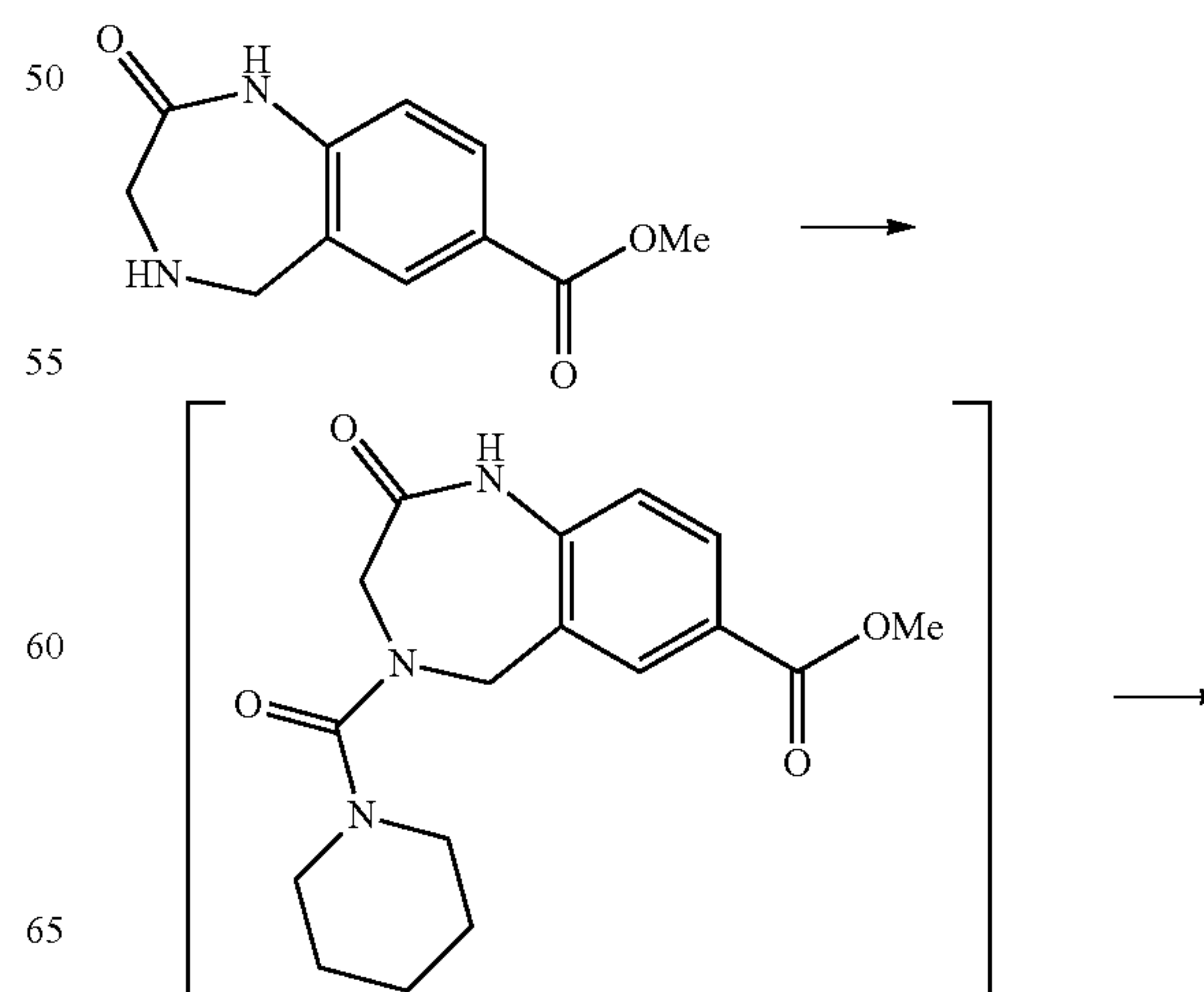
Step-2: N-Hydroxy-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide

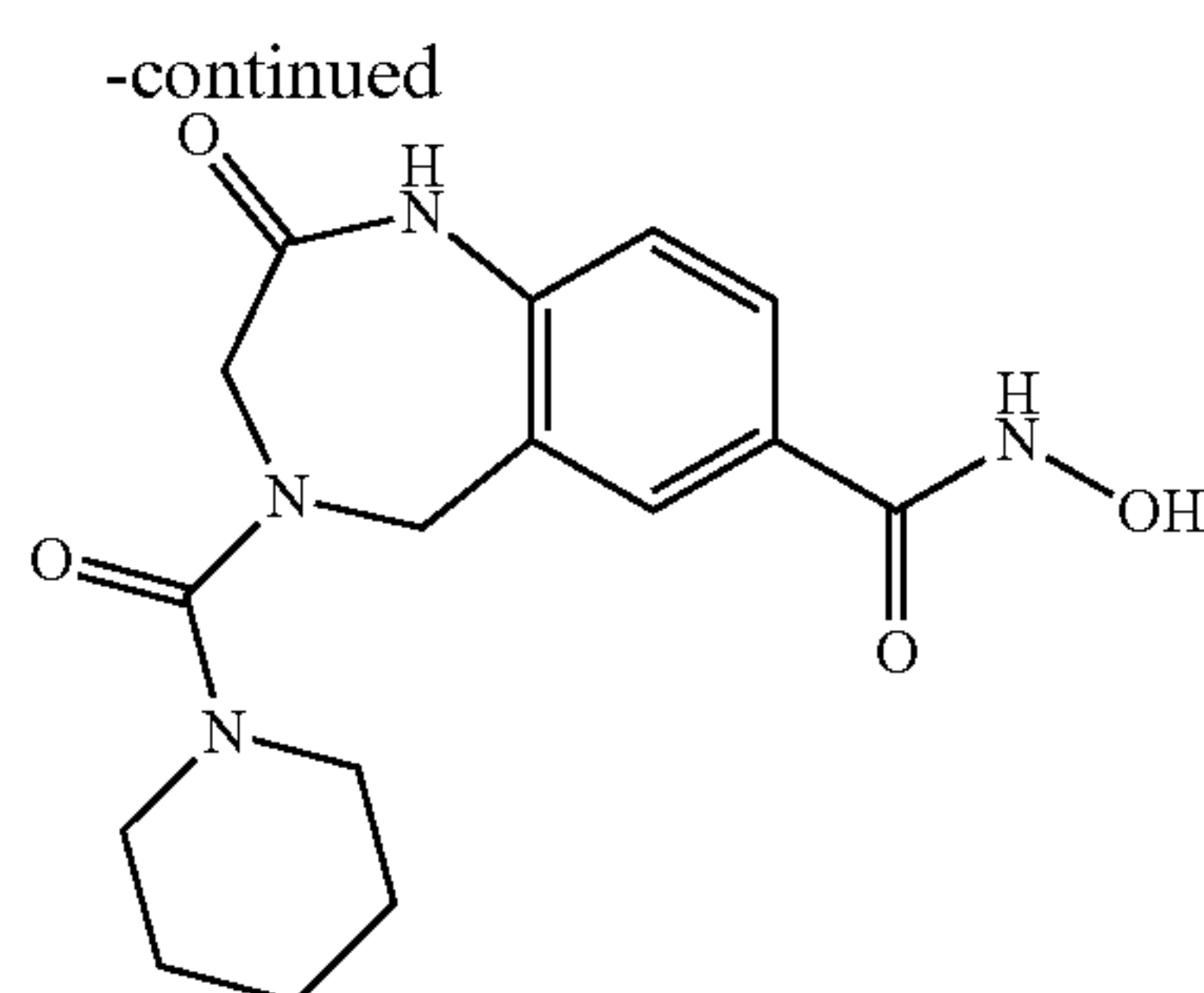


To a solution of methyl 2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (11.9 mg, 0.040 mmol) in MeOH (125  $\mu\text{L}$ ) and THF (500  $\mu\text{L}$ ) was added  $\text{NH}_2\text{OH}$  (50% in water, 209  $\mu\text{L}$ , 3.41 mmol, 85 equiv) and aq. 2N NaOH solution (40  $\mu\text{L}$ , 0.080 mmol, 2 equiv). The reaction was stirred at room temperature for 1 h and was directly purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5  $\mu\text{m}$ , 19 $\times$ 50 mm; Mobile Phase A: Water/0.1% Formic Acid; Mobile Phase B: MeCN/0.1% Formic Acid; Flow rate: 20 mL/min; Gradient: 5% B to 85% B in 7 min) to afford the title compound (3.3 mg, 28% yield).  $^1\text{H-NMR}$  (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 10.02 (s, 1 H), 8.25 (s, 1 H), 7.72-7.78 (m, 1 H), 7.04-7.23 (m, 2 H), 6.91-7.04 (m, 1 H), 6.79 (m, 2 H), 6.56-6.71 (m, 2 H), 4.77 (s, 2 H), 4.42 (s, 2 H). MS: (ES,  $m/z$ ): 298  $[\text{M}+\text{H}]^+$ .

## Example 75

Preparation of N-hydroxy-2-oxo-4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide

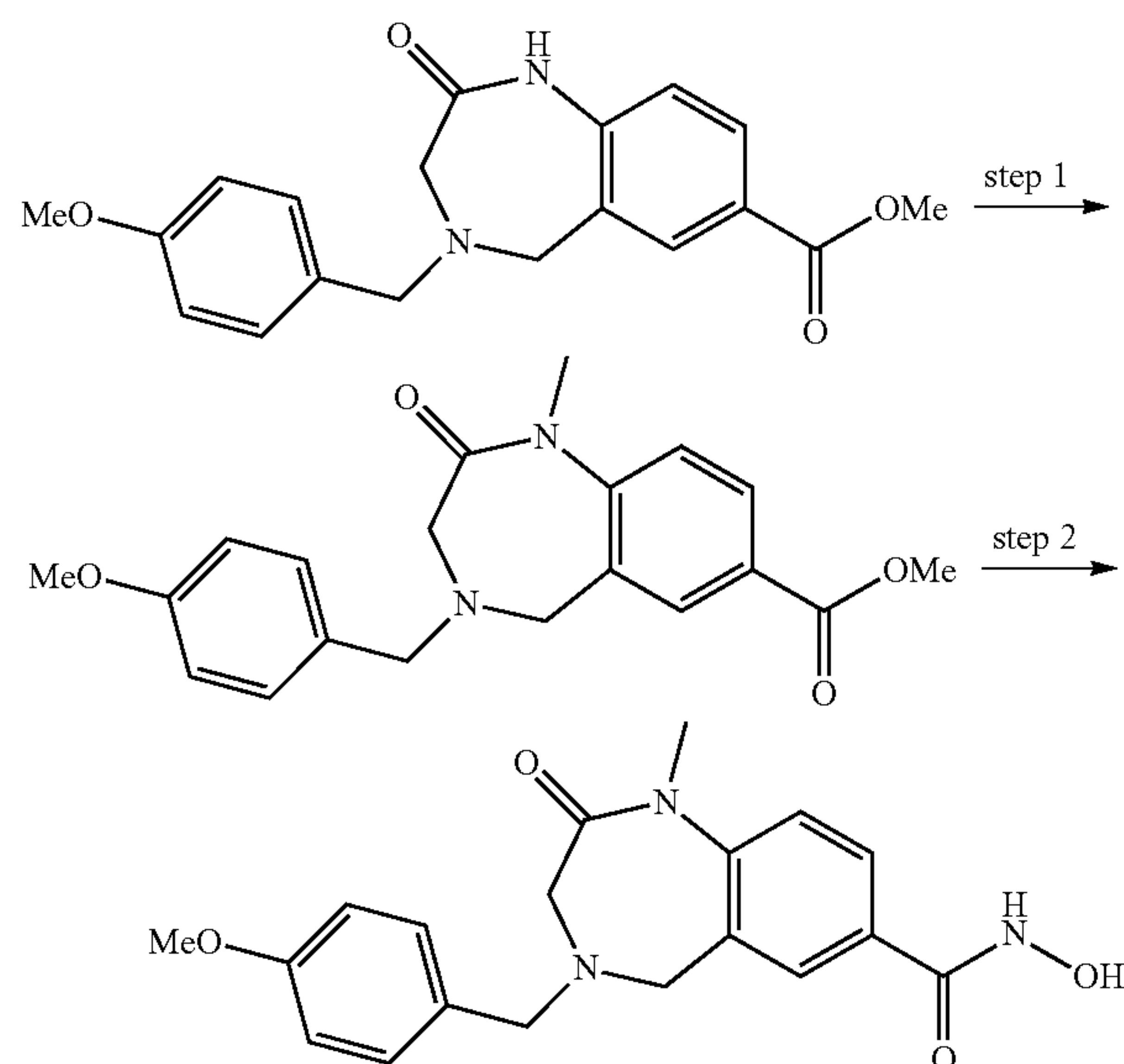


**221**

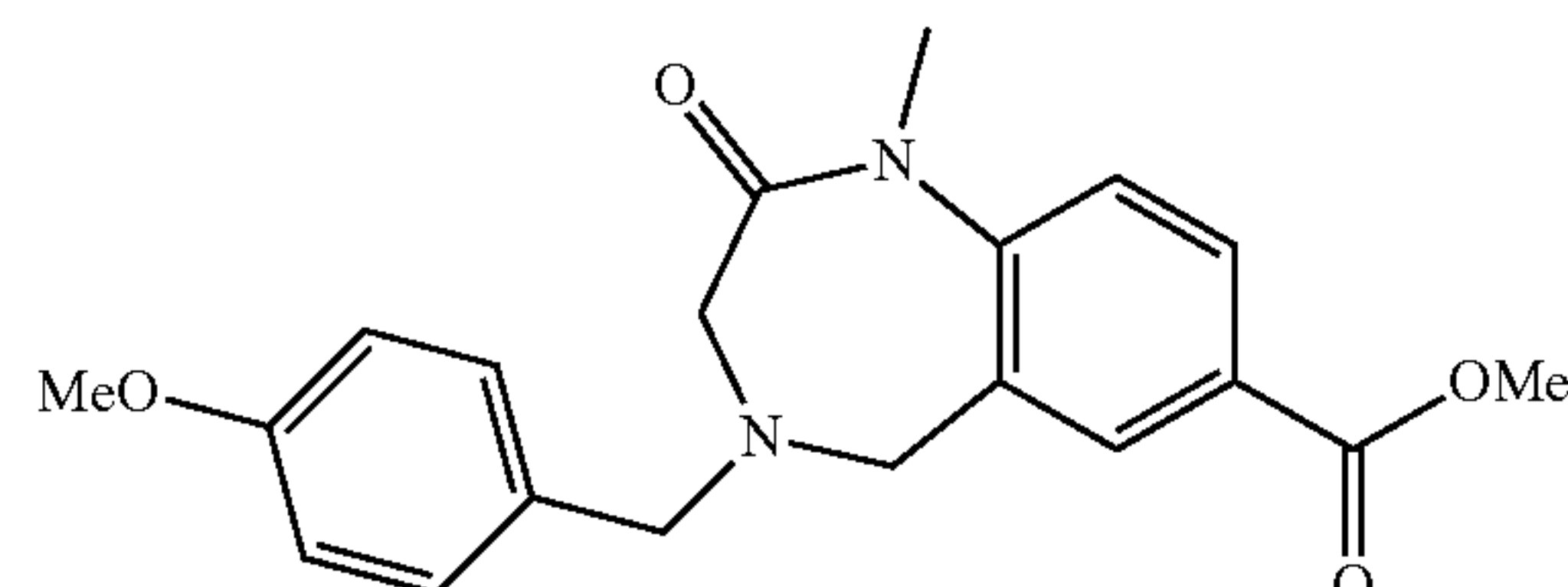
A 2-mL reaction vial was charged with ethyl 2-oxo-2,3,4,5-tetrahydro-1H -benzo[e][1,4]diazepine-7-carboxylate (11 mg, 0.05 mmol), bis(2,5-dioxopyrrolidin-1-yl) carbonate (14 mg, 0.055 mmol), MeCN (500  $\mu$ L) and Et<sub>3</sub>N (41.8  $\mu$ L, 0.3 mmol). The vial was sealed and shaken at room temperature for 1 h. The solvent was removed under a stream of nitrogen. DMA (500  $\mu$ L) and piperidine (neat, 29.6  $\mu$ L, 0.3 mmol) were added and the vial was shaken at room temperature overnight. The mixture was diluted with brine (500  $\mu$ L) and extracted with EtOAc (2 $\times$ 600  $\mu$ L). The combined organic layers was dried under a stream of nitrogen. A solvent mixture of THF/MeOH (3:1, 180  $\mu$ L) was added to the vial and it was shaken at 50° C. for 15 min to dissolve the residue. NH<sub>2</sub>OH (50% in water, 125  $\mu$ L) was added followed by aq. 1N NaOH (85 L) and the vial was sealed and shaken at room temperature overnight. The solvent was evaporated under reduce pressure. The residue was dissolved in DMSO (500  $\mu$ L), then purified by HPLC to afford the title compound (1.3 mg, 7.8% yield). MS: (ES, m/z): 333 [M+H]<sup>+</sup>.

## Example 76

Preparation of N-hydroxy-4-(4-methoxybenzyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide

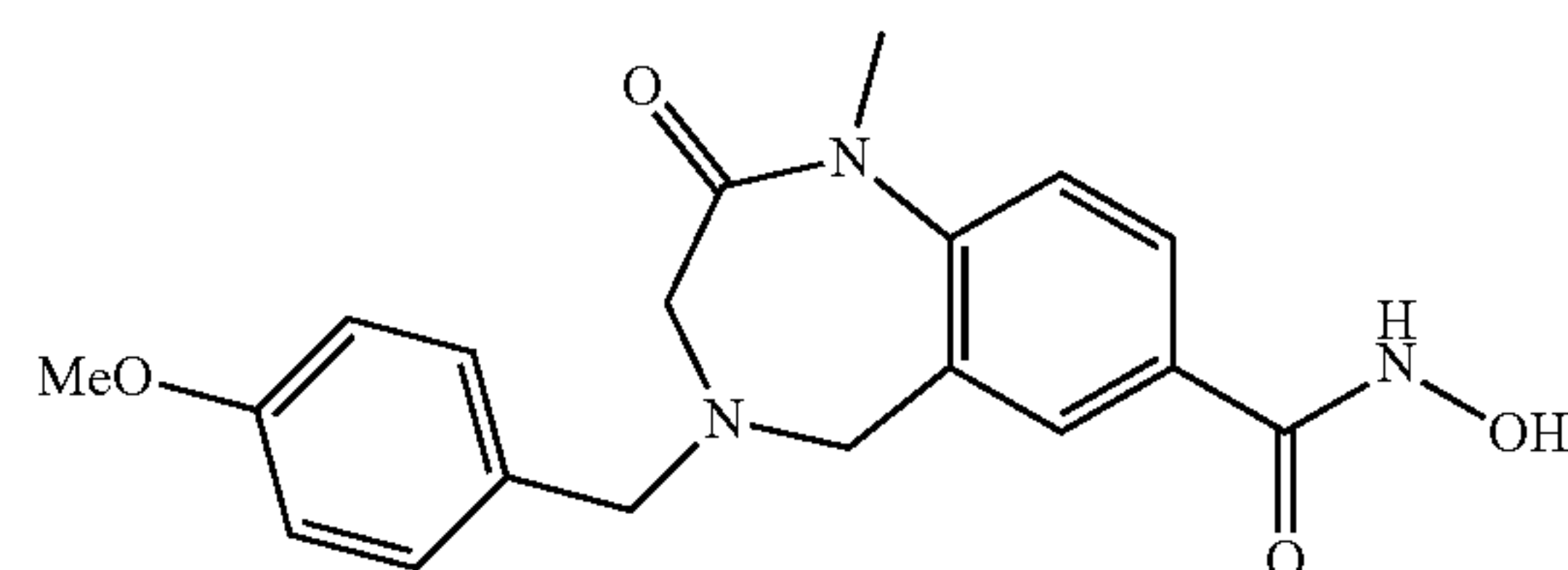
**222**

Step-1: Methyl 4-(4-methoxybenzyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H -benzo[e][1,4]diazepine-7-carboxylate



To a cooled solution of methyl 4-(4-methoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1H -benzo[e][1,4]diazepine-7-carboxylate (56.5 mg, 0.166 mmol, 1 equiv) in DMF (1.3 mL) was added sodium hydride (10.6 mg, 0.266 mmol, 1.6 equiv). After stirring for 15 minutes in cooling bath, the bath was removed and the reaction was stirred at room temperature for 15 minutes. Iodomethane (11.4  $\mu$ L, 0.183 mmol, 1.1 equiv) was added and the reaction was stirred at room temperature overnight. To the reaction mixture was added a saturated aqueous solution of NaHCO<sub>3</sub> and water. The resulting solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford the title compound (58 mg) which was used without further purification. MS: (ES, m/z): 355 [M+H]<sup>+</sup>.

Step-2: N-Hydroxy-4-(4-methoxybenzyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H -benzo[e][1,4]diazepine-7-carboxamide



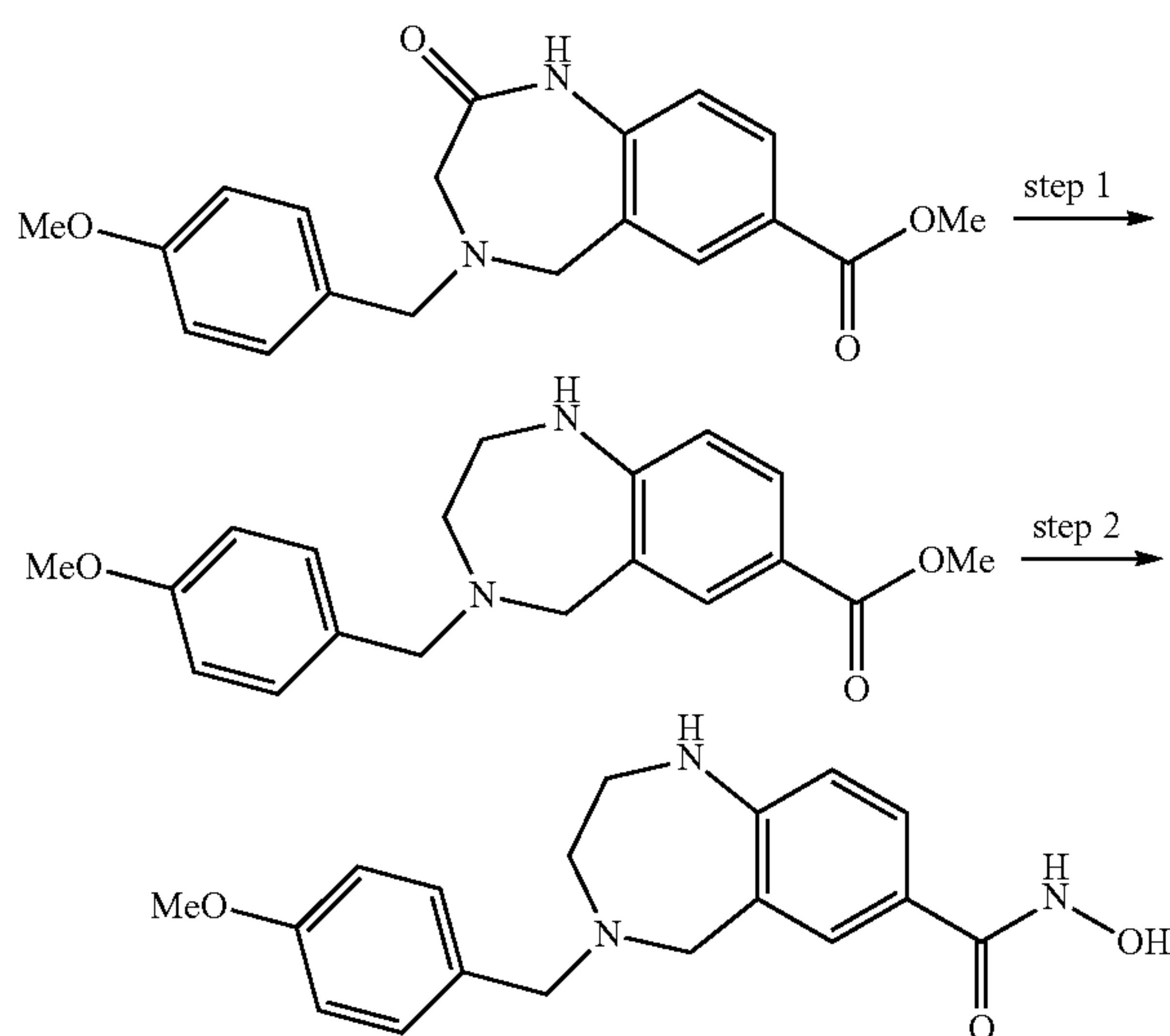
To a solution of methyl 4-(4-methoxybenzyl)-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H -benzo[e][1,4]diazepine-7-carboxylate (58 mg, 0.16 mmol, 1 equiv) in MeOH (300  $\mu$ L) and THF (1.2 mL) was added NH<sub>2</sub>OH (50% in water, 852  $\mu$ L, 13.9 mmol, 85 equiv) and aq. 2N NaOH solution (164  $\mu$ L, 0.327 mmol, 2 equiv). The reaction was stirred at room temperature for 2 h and was directly purified by Prep-HPLC (Column: Xbridge RP C18 OBD, 5  $\mu$ m, 19 $\times$ 50 mm; Mobile Phase A: Water/0.1% Formic Acid; Mobile Phase B: MeCN/0.1% Formic Acid; Flow rate: 20 mL/min; Gradient: 2% B to 50% B in 7 min) to afford the title compound (10.3 mg, 17% yield over 2 steps). <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$ (ppm): 11.21 (br s, 1H), 9.01 (br s, 1 H), 7.71-7.77 (m, 1 H), 7.62-7.65 (m, 1 H), 7.38 (d, J=8.5 Hz, 1 H), 7.21 (d, J=8.5 Hz, 2 H), 6.85 (d, J=8.5 Hz, 2 H), 3.68 (s, 3 H), 3.54 (s, 2 H), 3.48 (s, 2 H), 3.24 (s, 3 H). MS: (ES, m/z): 356 [M+H]<sup>+</sup>.



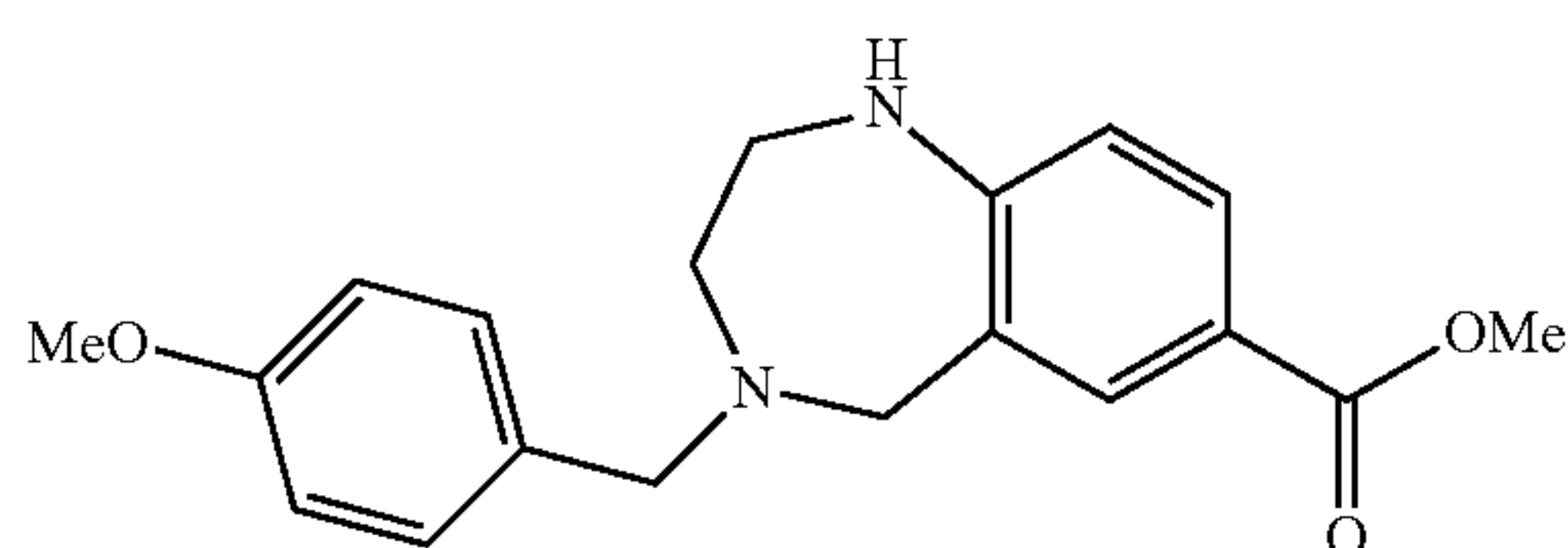
## 223

## Example 77

Preparation of N-Hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide

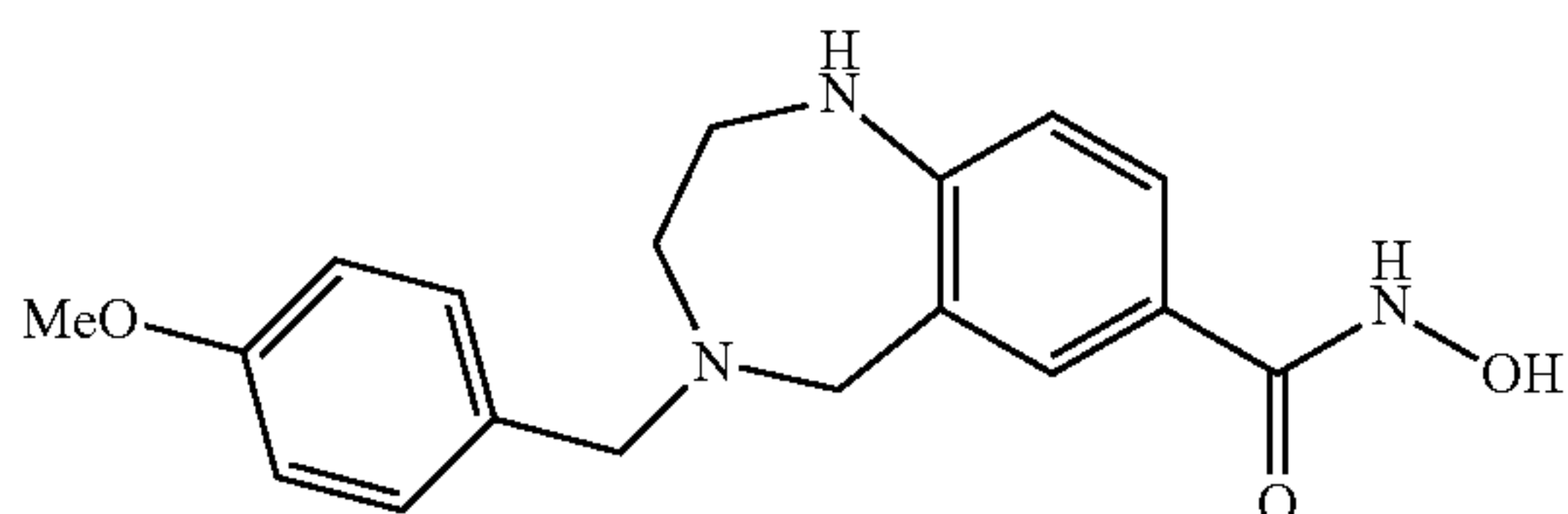


Step-1: Methyl 4-(4-methoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate



To a suspension of methyl 4-(4-methoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (101 mg, 0.298 mmol, 1 equiv) in toluene (3 mL) was added borane-methyl sulfide complex (164  $\mu$ L, 0.328 mmol, 1.1 equiv). The mixture was heated to reflux for 5 h, then cooled to room temperature. Methanol was added and the reaction was stirred for 10 min at room temperature and then for 15 min at reflux. The reaction mixture was concentrated and purified by silica gel chromatography (Gradient 0-5% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to afford the title compound (83 mg, 85% yield). MS: (ES, m/z): 327  $[\text{M}+\text{H}]^+$ .

Step-2: N-Hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide

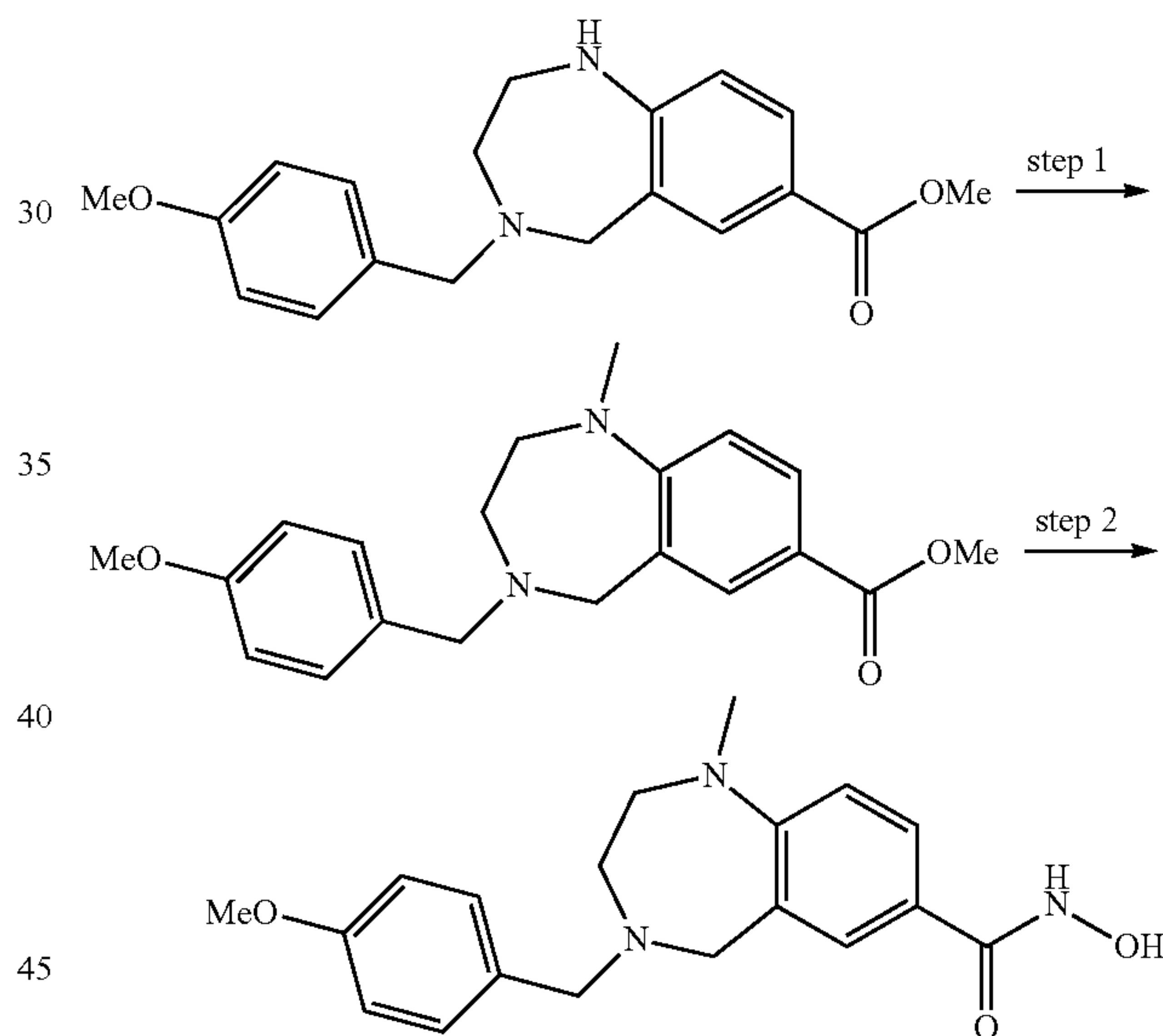


## 224

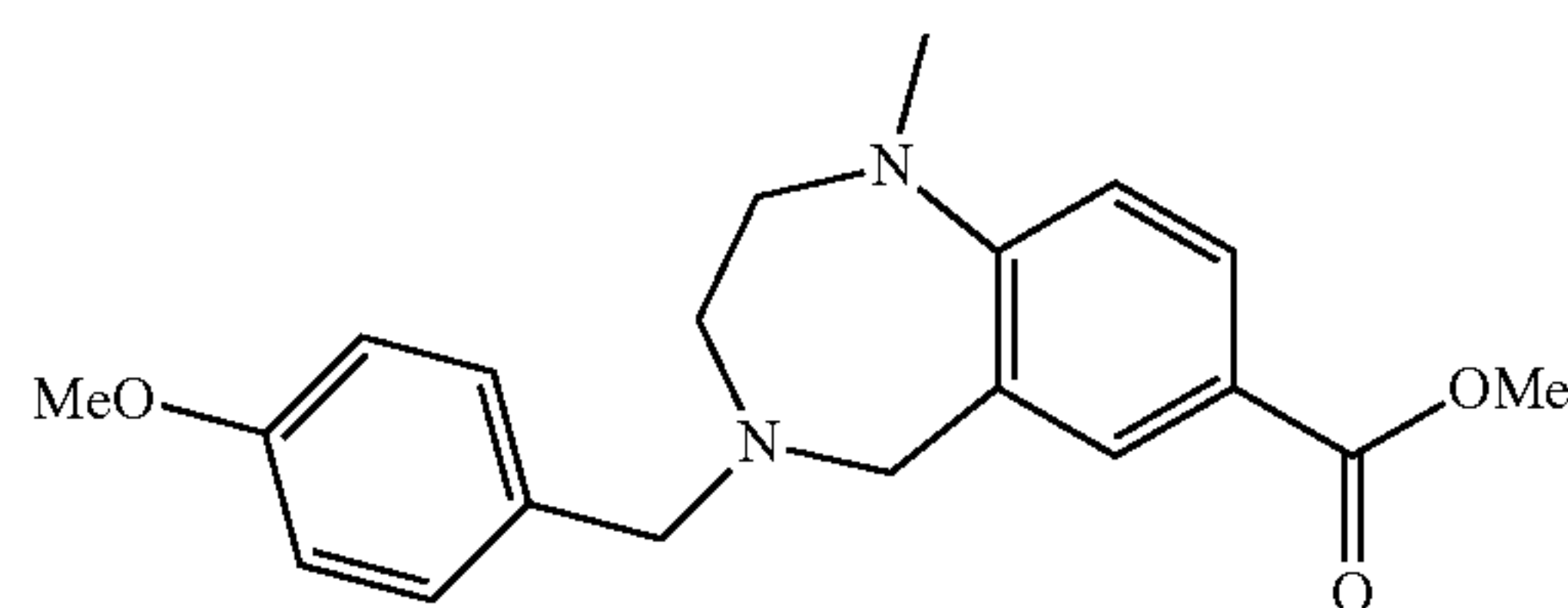
To a solution of methyl 4-(4-methoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (83 mg, 0.254 mmol, 1 equiv) in MeOH (250  $\mu$ L) and THF (1 mL) was added  $\text{NH}_2\text{OH}$  (50% in water, 1.33 mL, 21.6 mmol, 85 equiv) and aq. 2N NaOH solution (254  $\mu$ L, 0.509 mmol, 2 equiv). The reaction was stirred at room temperature for 3 h and was directly purified by Prep-HPLC (Column: Xbridge RP C18 OBD, 5  $\mu$ m, 19 $\times$ 50 mm; Mobile Phase A: Water/0.1% Formic Acid; Mobile Phase B: MeCN/0.1% Formic Acid; Flow rate: 20 mL/min; Gradient: 2% B to 50% B in 7 min) to afford the title compound (11.3 mg, 14% yield).  $^1\text{H-NMR}$  (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$ (ppm): 8.39 (br s, 1 H), 7.52-7.61 (m, 2 H), 7.41 (br d,  $J=8.2$  Hz, 2 H), 7 (d,  $J=8.2$  Hz, 2 H), 6.90 (d,  $J=8.2$  Hz, 1 H), 4.20 (br d,  $J=9.1$  Hz, 2 H), 3.82 (s, 3 H), 3.25-3.42 (m, 4 H). MS: (ES, m/z): 328  $[\text{M}+\text{H}]^+$ .

## Example 78

Preparation of N-Hydroxy-4-(4-methoxybenzyl)-1-methyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide



Step-1: Methyl 4-(4-methoxybenzyl)-1-methyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate

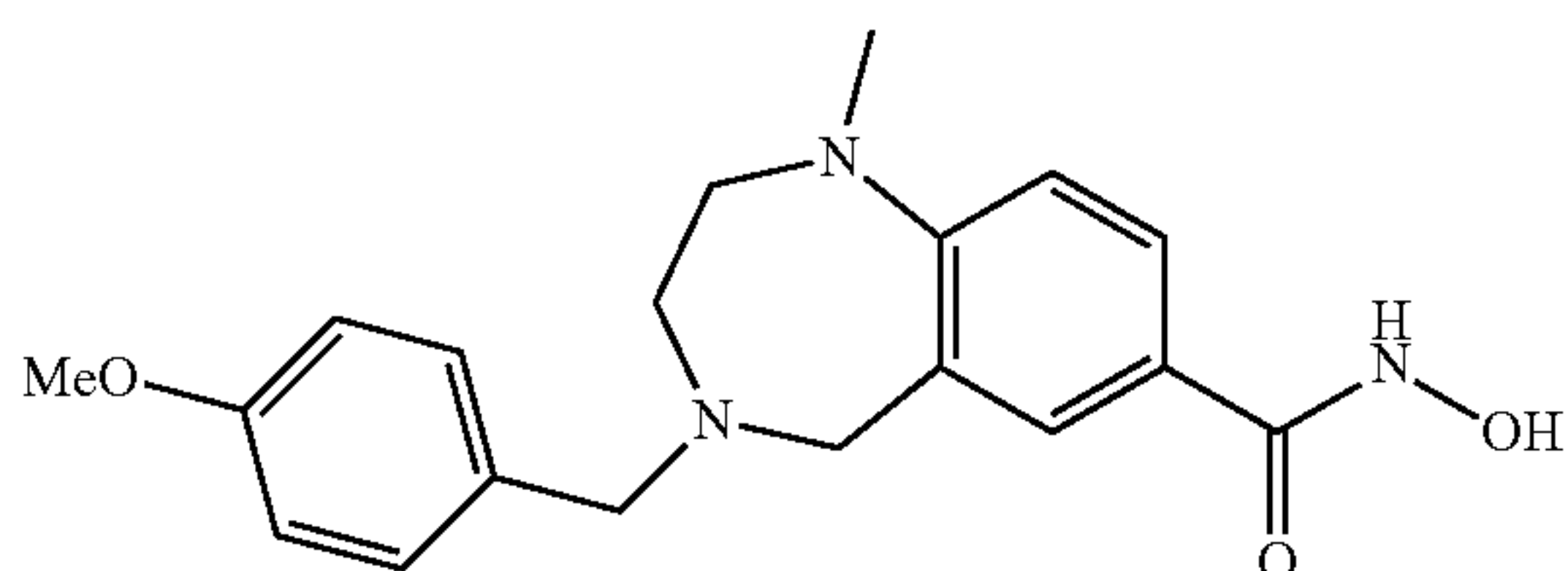


To a solution of methyl 4-(4-methoxybenzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (60.7 mg, 0.186 mmol, 1 equiv) in MeCN (2 mL) was added  $\text{Cs}_2\text{CO}_3$  (60.6 mg, 0.186 mmol, 1 equiv), and methyl iodide

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(0.014 mL, 0.223 mmol, 1.2 equiv). The reaction was stirred at room temperature for 7 h. Water was added to the reaction and the layers were separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification by silica gel chromatography afforded the title compound (34 mg, 54% yield). MS: (ES,  $m/z$ ): 341  $[\text{M}+\text{H}]^+$ .

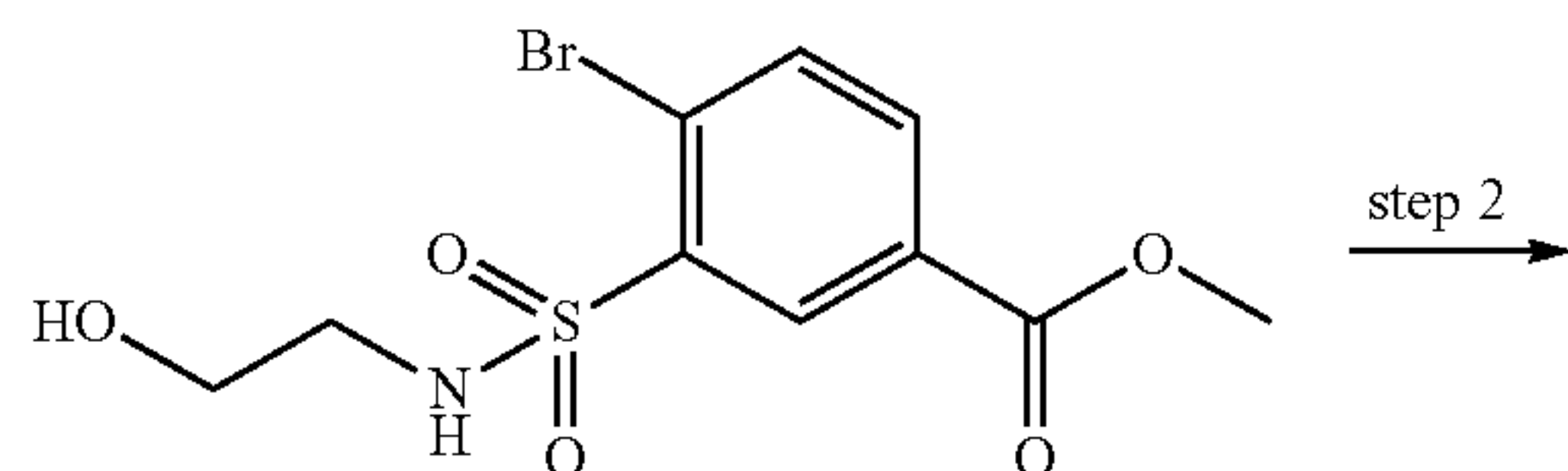
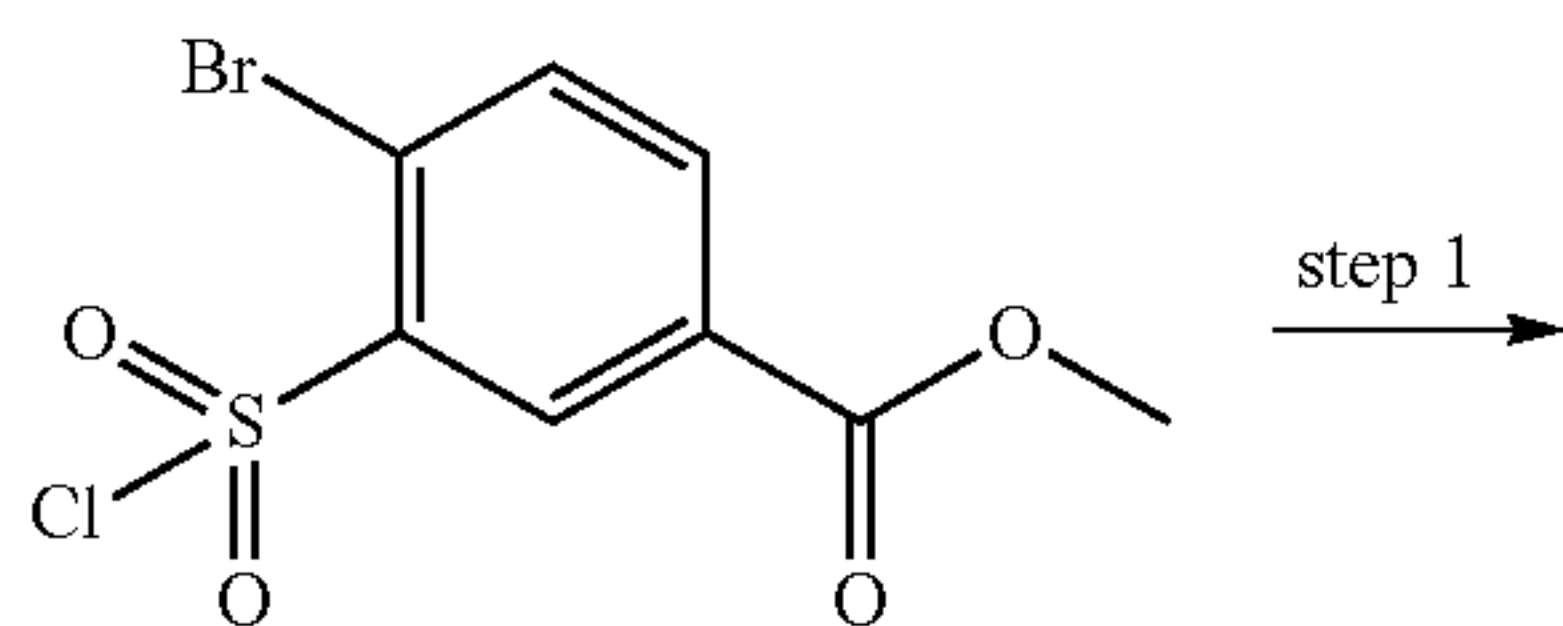
Step-2: N-Hydroxy-4-(4-methoxybenzyl)-1-methyl-2,3,4,5-tetrahydro-1H -benzo[e][1,4]diazepine-7-carboxamide



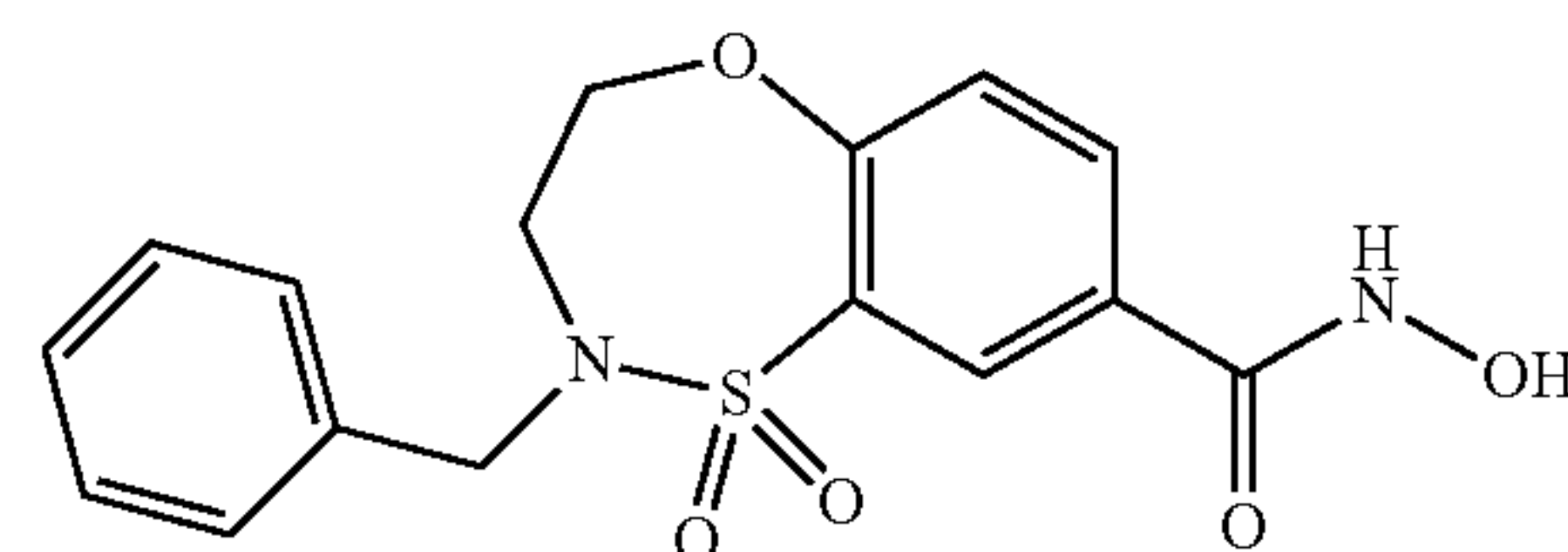
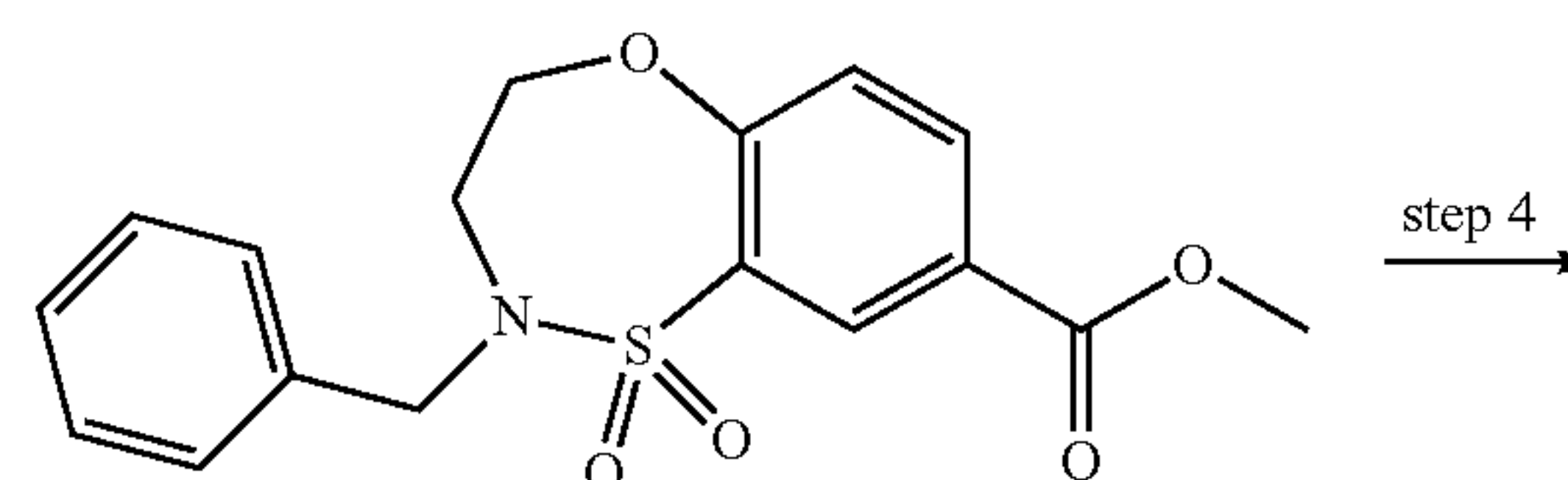
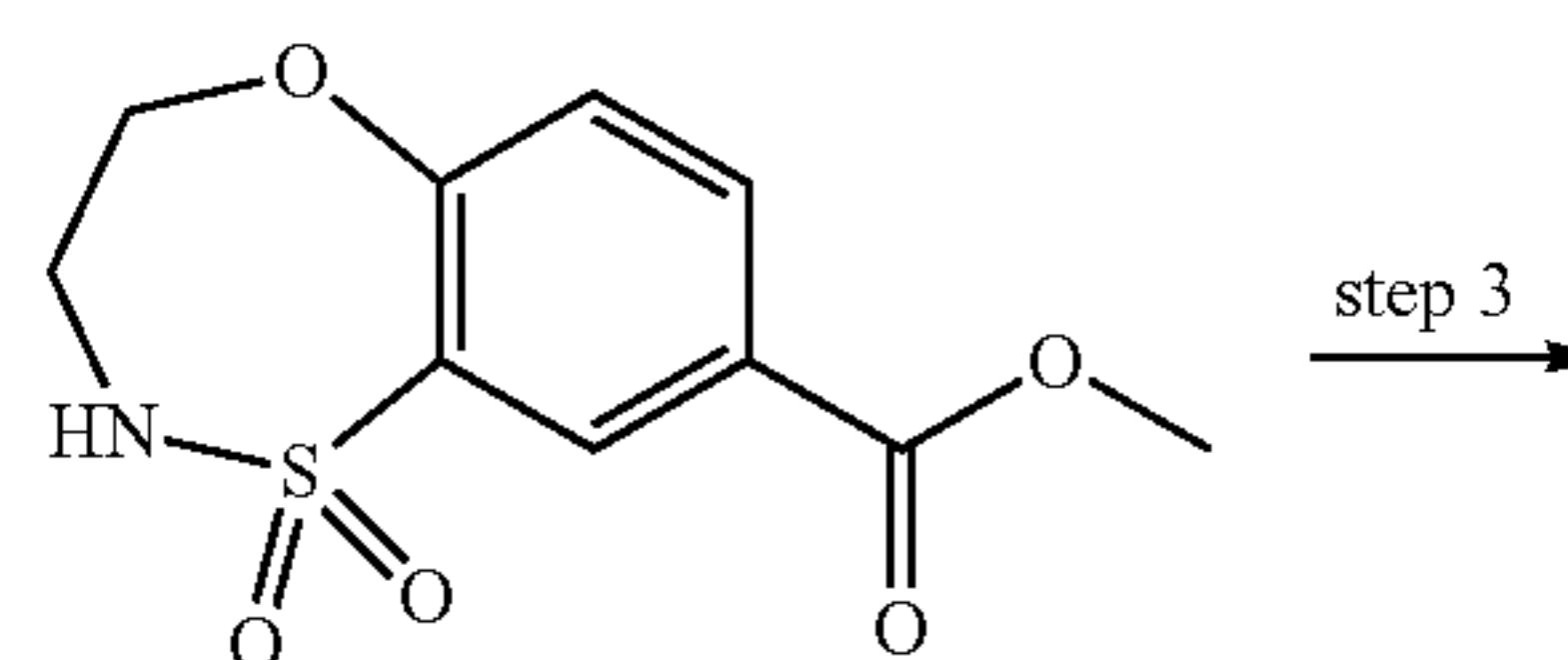
To a solution of methyl 4-(4-methoxybenzyl)-1-methyl-2,3,4,5-tetrahydro-1H -benzo[e][1,4]diazepine-7-carboxylate (34.1 mg, 0.100 mmol, 1 equiv) in MeOH (250  $\mu\text{L}$ ) and THF (1 mL) was added  $\text{NH}_2\text{OH}$  (50% in water, 522  $\mu\text{L}$ , 8.51 mmol, 85 equiv) and aq. 2N NaOH solution (100  $\mu\text{L}$ , 0.2 mmol, 2 equiv). The reaction was stirred at room temperature overnight and concentrated. Purification by Prep-HPLC (Column: Xbridge RP C18 OBD, 5  $\mu\text{m}$ , 19 $\times$ 50 mm; Mobile Phase A: Water/0.05% formic acid; Mobile Phase B: MeCN/0.05% formic acid; Flow rate: 23 mL/min; Gradient: 0% B to 35% B in 8 min; Detector, UV 254, 220 nm) afforded the title compound. MS: (ES,  $m/z$ ): 342  $[\text{M}+\text{H}]^+$ .

**Example 79**

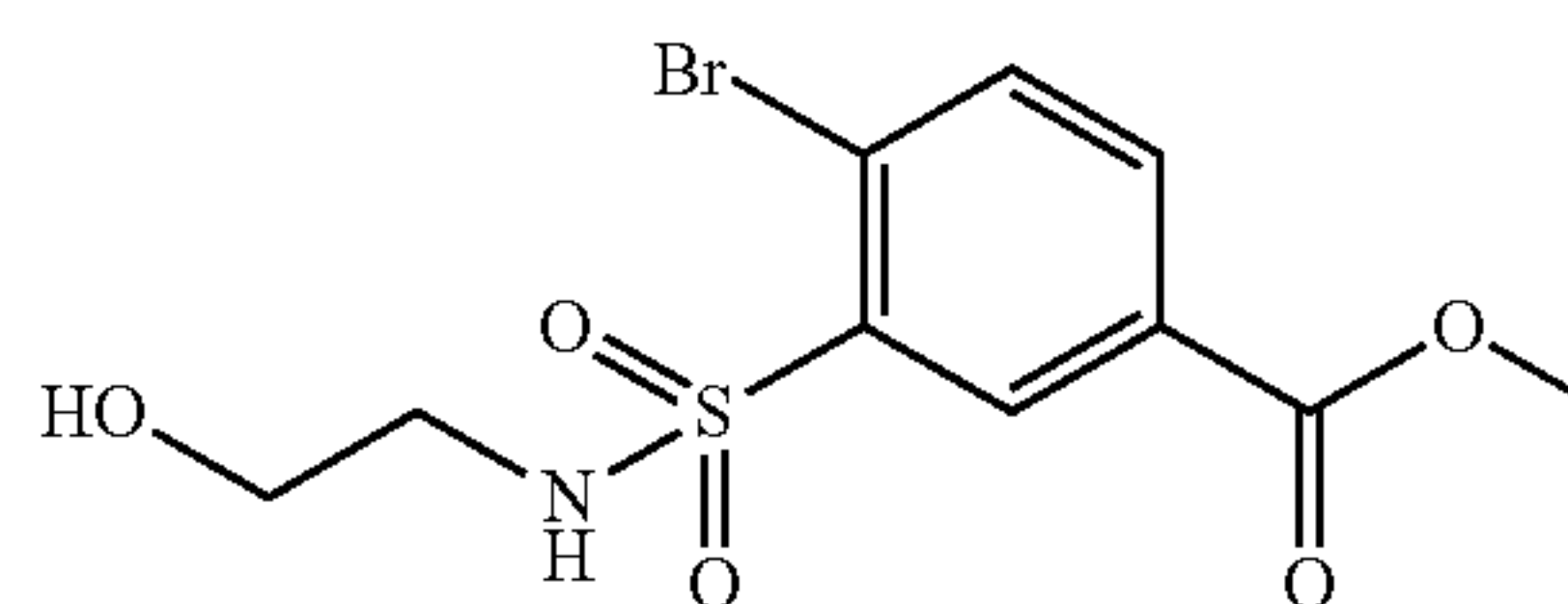
Preparation of 2-benzyl-N-hydroxy-3,4-dihydro-2H -benzo[b][1,4,5]oxathiazepine-8-carboxamide 1,1-dioxide

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-continued



Step-1: Methyl 4-bromo-3-(N-(2-hydroxyethyl)sulfamoyl)benzoate

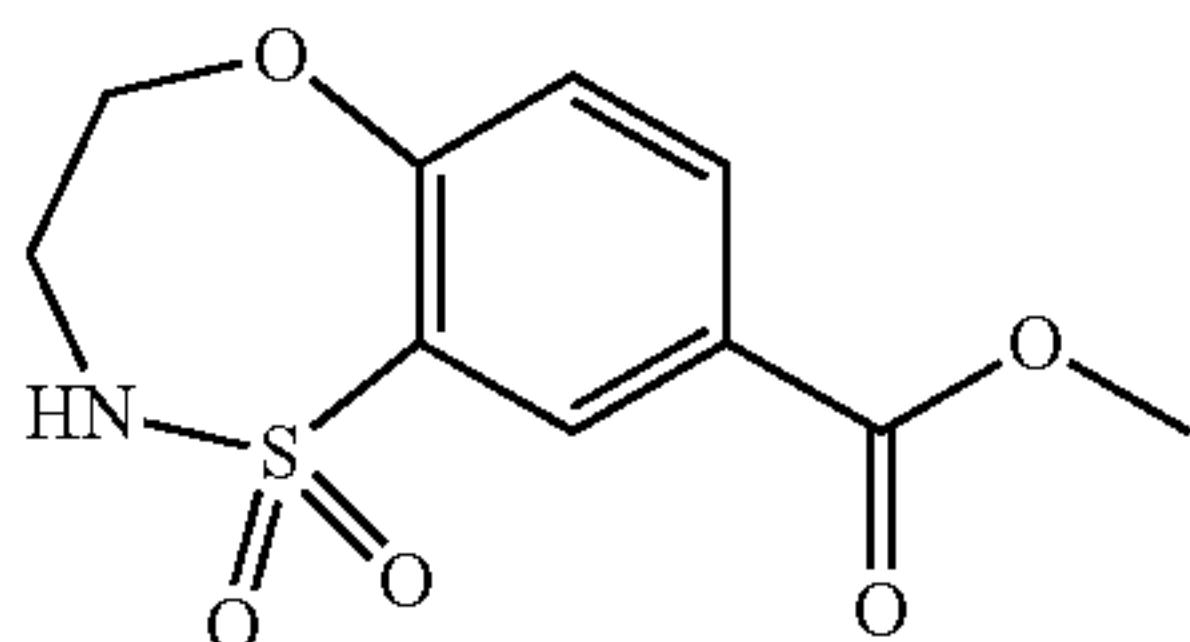


Into a 100-mL round-bottom flask, was placed methyl 4-bromo-3-(chlorosulfonyl)benzoate (100 mg, 0.32 mmol, 1 equiv), THF (2 mL), water (0.5 mL), magnesium oxide (0.06 g) and 2-aminoethan-1-ol (22 mg, 0.36 mmol, 1.1 equiv). The resulting mixture was stirred overnight at room temperature concentrated under vacuum. The residue was diluted with  $\text{H}_2\text{O}$  (50 mL). The resulting solution was extracted with EtOAc (3 $\times$ 50 mL) and dried over anhydrous sodium sulfate. The solid was filtered out. The filtrate was concentrated under vacuum to afford the title compound as a white solid (57 mg, 53% yield) which was used without further purification. MS: (ES,  $m/z$ ): 336  $[\text{M}-\text{H}]^-$ .



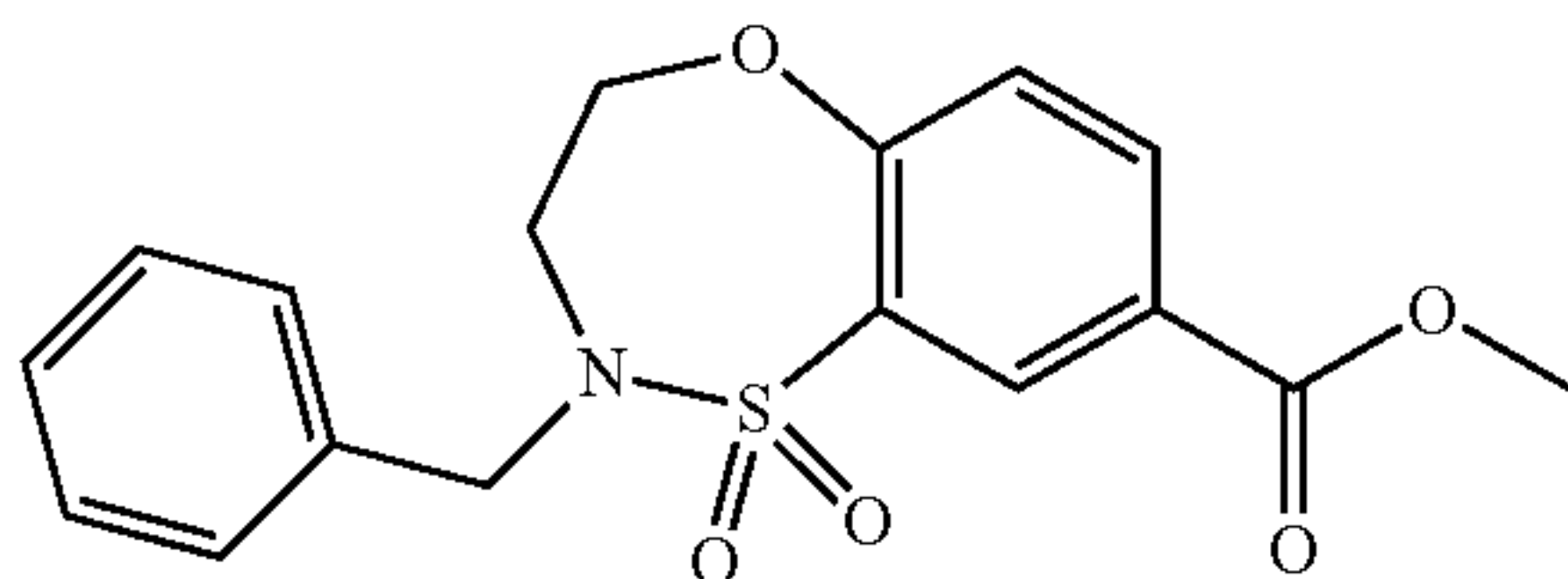
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Step-2: Methyl 3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine-8-carboxylate 1,1-dioxide



Into a 100-mL round-bottom flask, was placed methyl 4-bromo-3-(N-(2-hydroxyethyl)sulfamoyl)benzoate (350 mg, 1.03 mmol, 1 equiv), MeOH (2 mL), 1-methyl-2-pyrrolidinone (10 mL) and sodium methylate (70 mg, 1.30 mmol, 1.25 equiv). The resulting mixture was stirred 1h at room temperature. To the above mixture was added CuI (16 mg, 0.08 mmol, 0.08 equiv). The resulting solution was stirred overnight at 110° C. The resulting mixture was washed with H<sub>2</sub>O (30 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×30 mL) and dried over anhydrous sodium sulfate. The solid was filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography (EtOAc/pet. ether, 1:3) to afford the title compound as a yellow oil (250 mg, 93% yield). MS: (ES, m/z): 256 [M-H]<sup>-</sup>.

Step-3: Methyl 2-benzyl-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine-8-carboxylate 1,1-dioxide

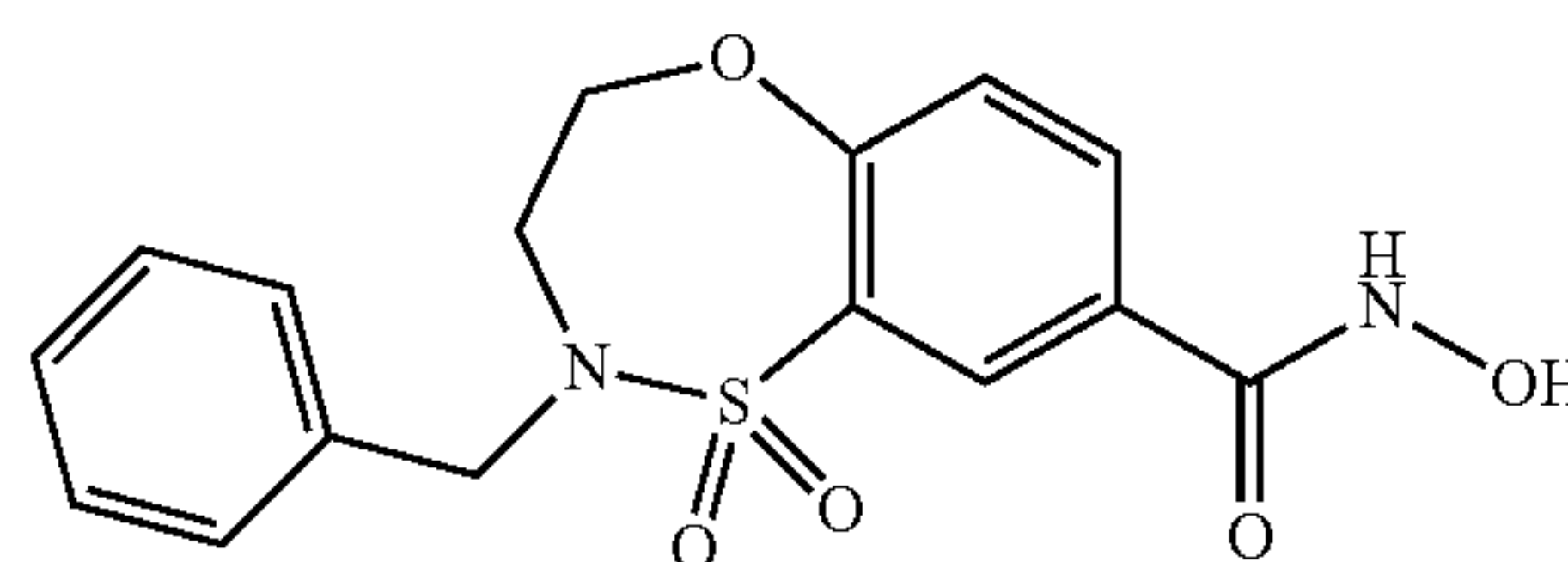


Into a 100-mL round-bottom flask, was placed methyl 3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine-8-carboxylate 1,1-dioxide (50 mg, 0.19 mmol, 1 equiv), DMF (3 mL), sodium hydride (9 mg, 0.38 mmol, 1.9 equiv), (bromomethyl)benzene (48 mg, 0.28 mmol, 1.4 equiv). The resulting

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mixture was stirred for 2 h at room temperature and then diluted with H<sub>2</sub>O (20 mL). The resulting solution was extracted with EtOAc (2×40 mL), washed with H<sub>2</sub>O (2×30 mL), and dried over anhydrous sodium sulfate. The solid was filtered out. The filtrate was concentrated under vacuum to afford the title compound as a yellow oil (87 mg) which was used without further purification.

Step-4: 2-Benzyl-N-hydroxy-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine-8-carboxamide 1,1-dioxide



Into a 100-mL round-bottom flask, was placed methyl 2-benzyl-3,4-dihydro-2H -benzo[b][1,4,5]oxathiazepine-8-carboxylate 1,1-dioxide (87 mg, 0.25 mmol, 1 equiv), THF (2 mL), MeOH (0.5 mL), aq. 1N NaOH (0.4 mL) and NH<sub>2</sub>OH (50% in water, 800 mg, 24.22 mmol). The resulting solution was stirred for 1 h at room temperature. The pH value of the solution was adjusted to 3 with 1N HCl. The crude product was purified by Prep-HPLC (Column: Xbridge Prep C18 OBD, 5 μm, 19×50 mm; Mobile Phase A: Water/0.3% formic acid; Mobile Phase B: MeCN; Flow rate: 23 mL/min; Gradient: 18% B to 59% B in 6 min, up to 100% B in 0.1 min, hold 0.9 min; Detector, UV 254, 220 nm) to afford the title compound as a white solid (9.6 mg, 11% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 8.18 (d, 1H), 7.80-7.97 (q, 1H), 7.39-7.30 (m, 6H), 4.29-4.27 (t, 2H, J=4.0 Hz), 4.20 (s, 2H), 3.56-3.54 (t, 2H, J=4.4 Hz). MS: (ES, m/z): 349[M+H]<sup>+</sup>.

TABLE 35

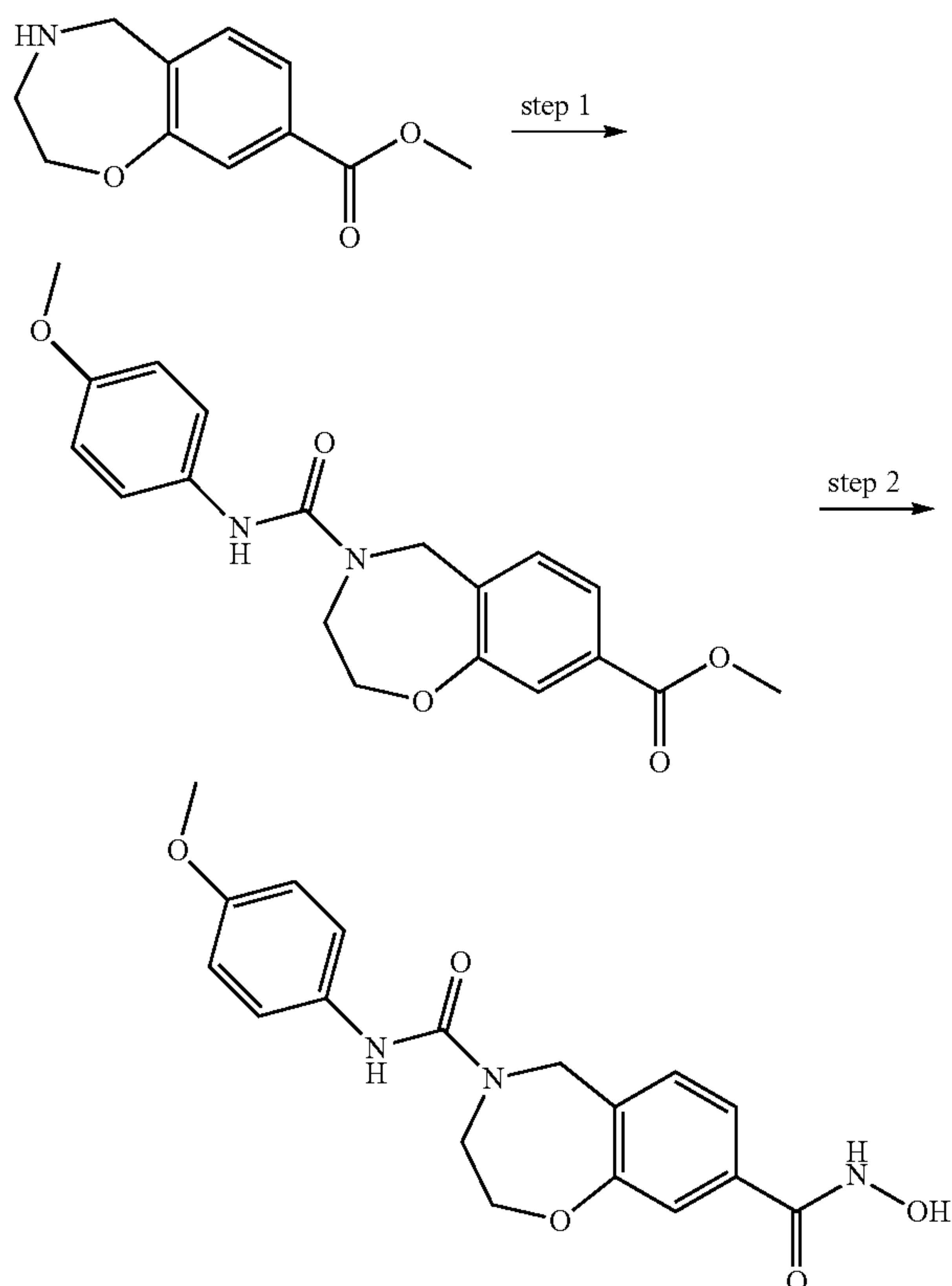
The following compound was prepared according to the method of Example 79.

Structure	Found M + H	<sup>1</sup> H-NMR (400 MHz, DMSO-d <sub>6</sub> ) δ(ppm)
	(ES, m/z): 11.40 (s, 1H), 9.30 (s, 1H), 7.86 (d, 1H), 7.72-7.69 (m, 349 1H), 7.60 (d, 1H), 7.39-7.31 (m, 5H), 4.28-4.18 (m, [M + H] <sup>+</sup> 4H), 3.55-3.53 (t, 2H, J = 4.0 Hz)	

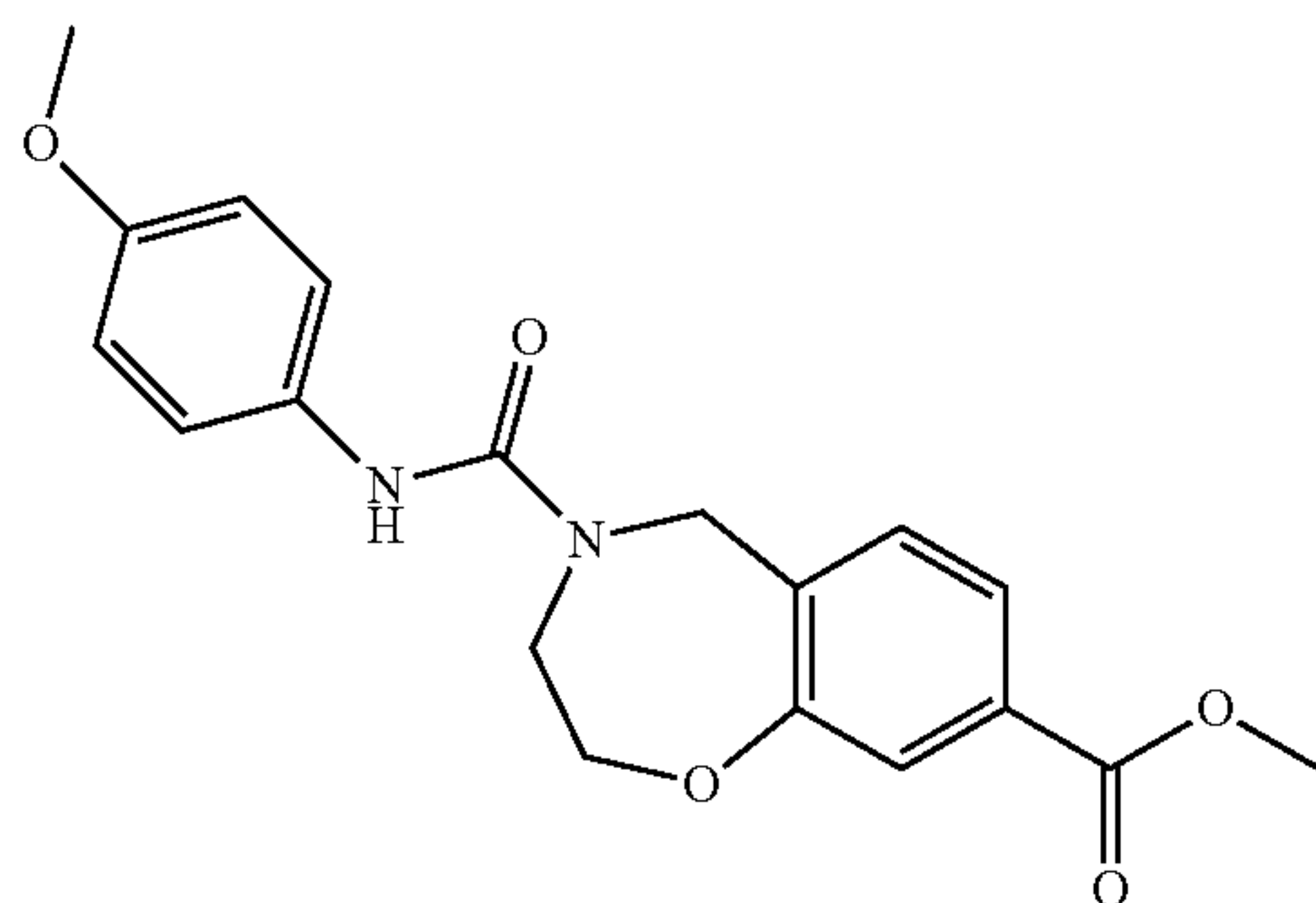
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## Example 80

Preparation of N8-hydroxy-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



Step-1: Methyl 4-((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

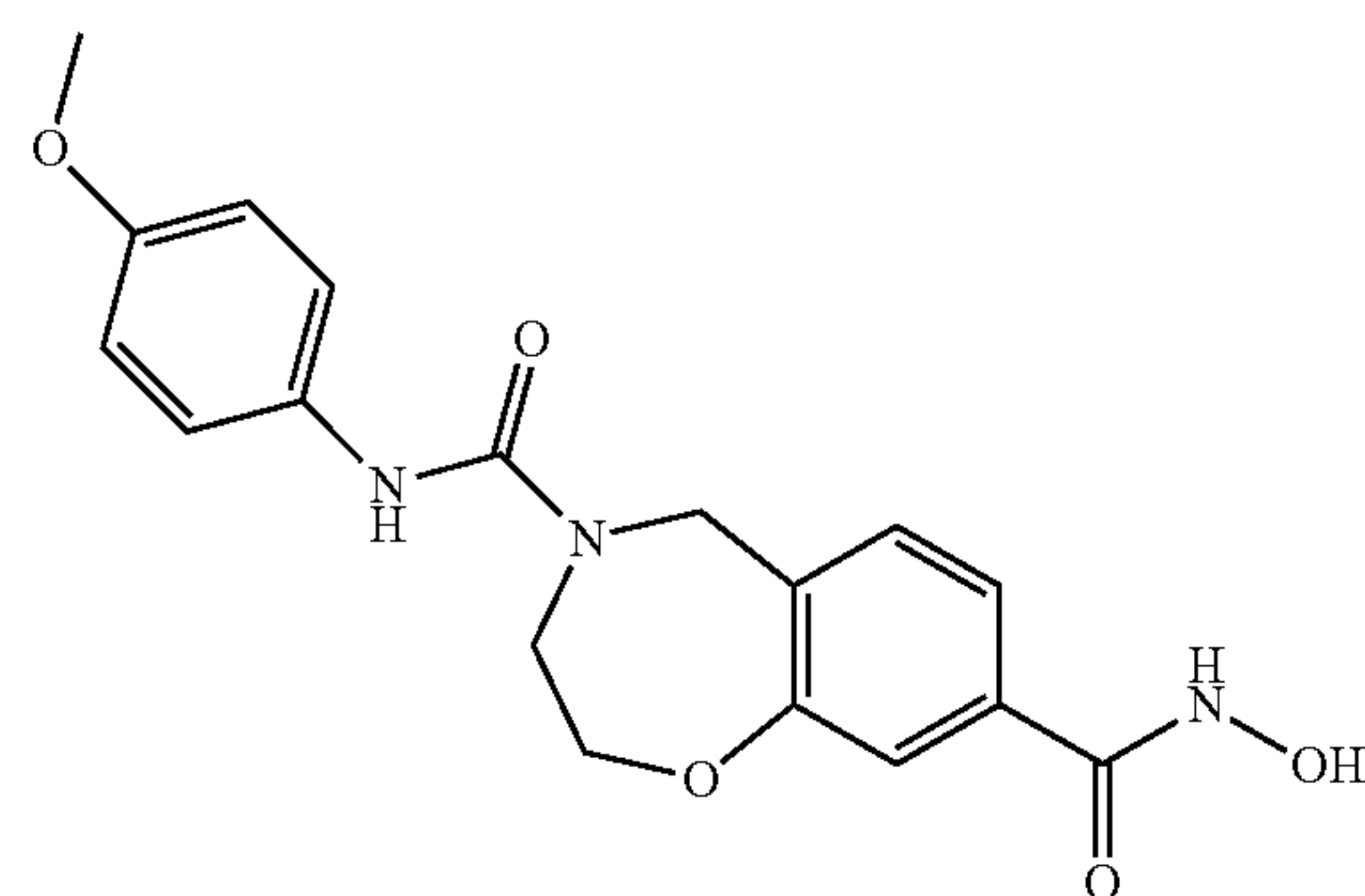


A 2 mL reaction vial was charged with methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (0.2 M in 1,2-dichloroethane, 150  $\mu$ L, 30  $\mu$ mol) and triethylamine (neat, 10  $\mu$ L, 71  $\mu$ mol). 1-Isocyanato-4-methoxybenzene (0.2 M in dioxane, 195  $\mu$ L, 39  $\mu$ mol) was added and the vial was sealed and shaken at room temperature overnight. The reaction mixture was diluted with brine (500  $\mu$ L) and

## 230

extracted with EtOAc (2 $\times$ 500  $\mu$ L). The combined organic layers were evaporated to dryness under reduced pressure.

Step-2: N8-Hydroxy-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide

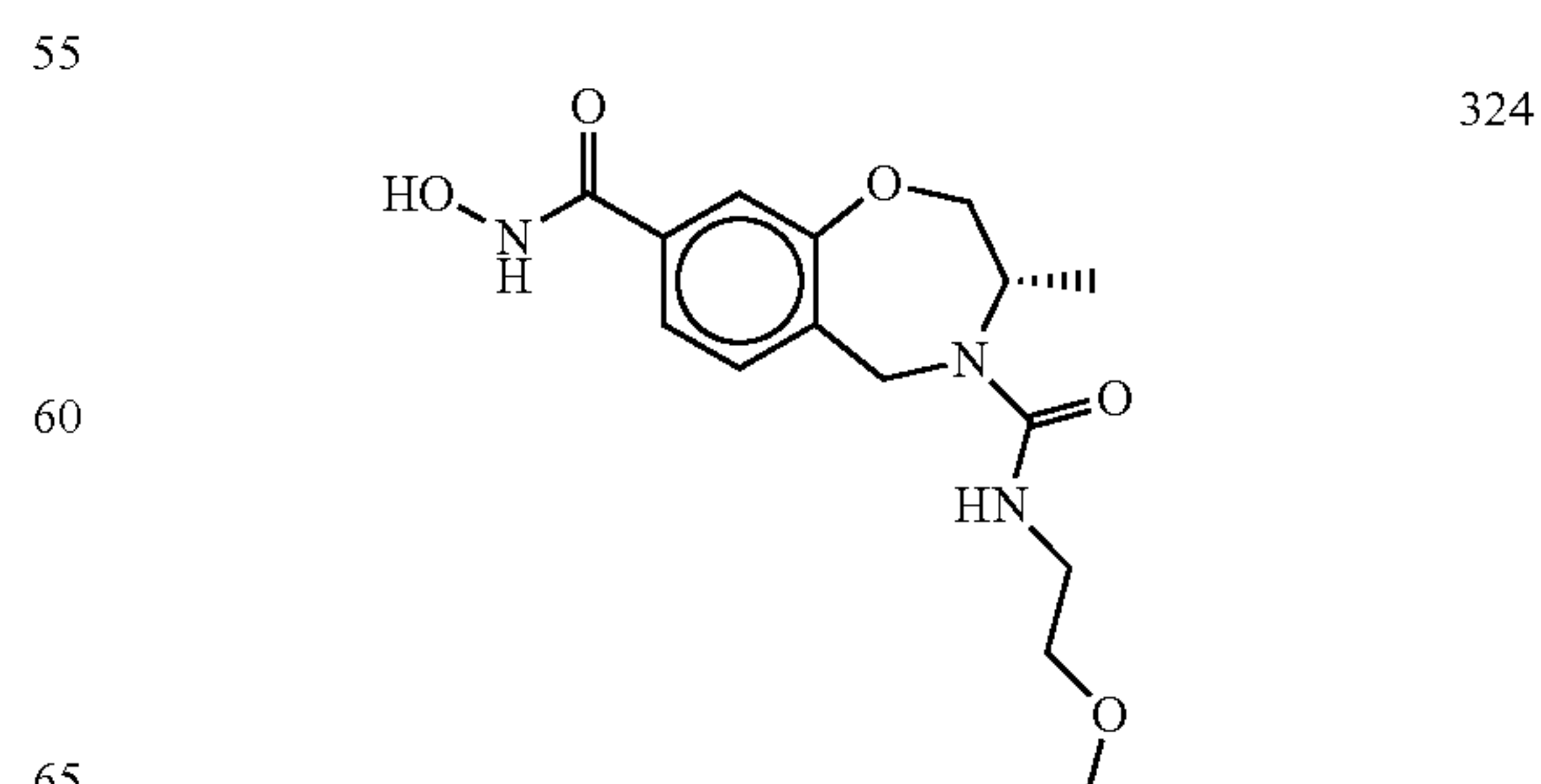
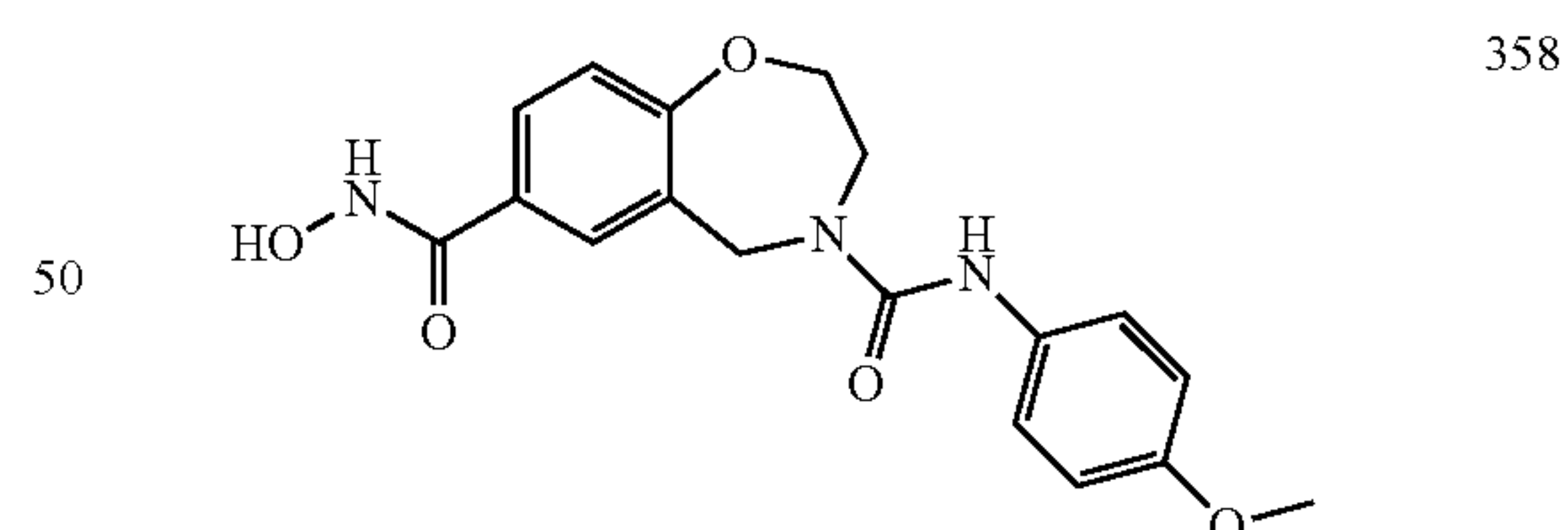


Mixed solvent of THF/MeOH (3:1, 180  $\mu$ L) was added to the vial containing methyl 4-((4-methoxyphenyl)carbamoyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate and it was shaken at 50° C. for 15 min to dissolve the residue.  $\text{NH}_2\text{OH}$  (50% in water, 125  $\mu$ L) was added, followed by aq. 1N NaOH (85  $\mu$ L) and the vial was sealed and shaken at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in DMSO (500  $\mu$ L), then purified by HPLC to afford the title compound (9.3 mg, 87% yield). MS: (ES,  $m/z$ ): 358  $[\text{M}+\text{H}]^+$ .

TABLE 36

The following compound was prepared by the parallel synthesis method of Example 80.

Structure	Found M + H (ES)
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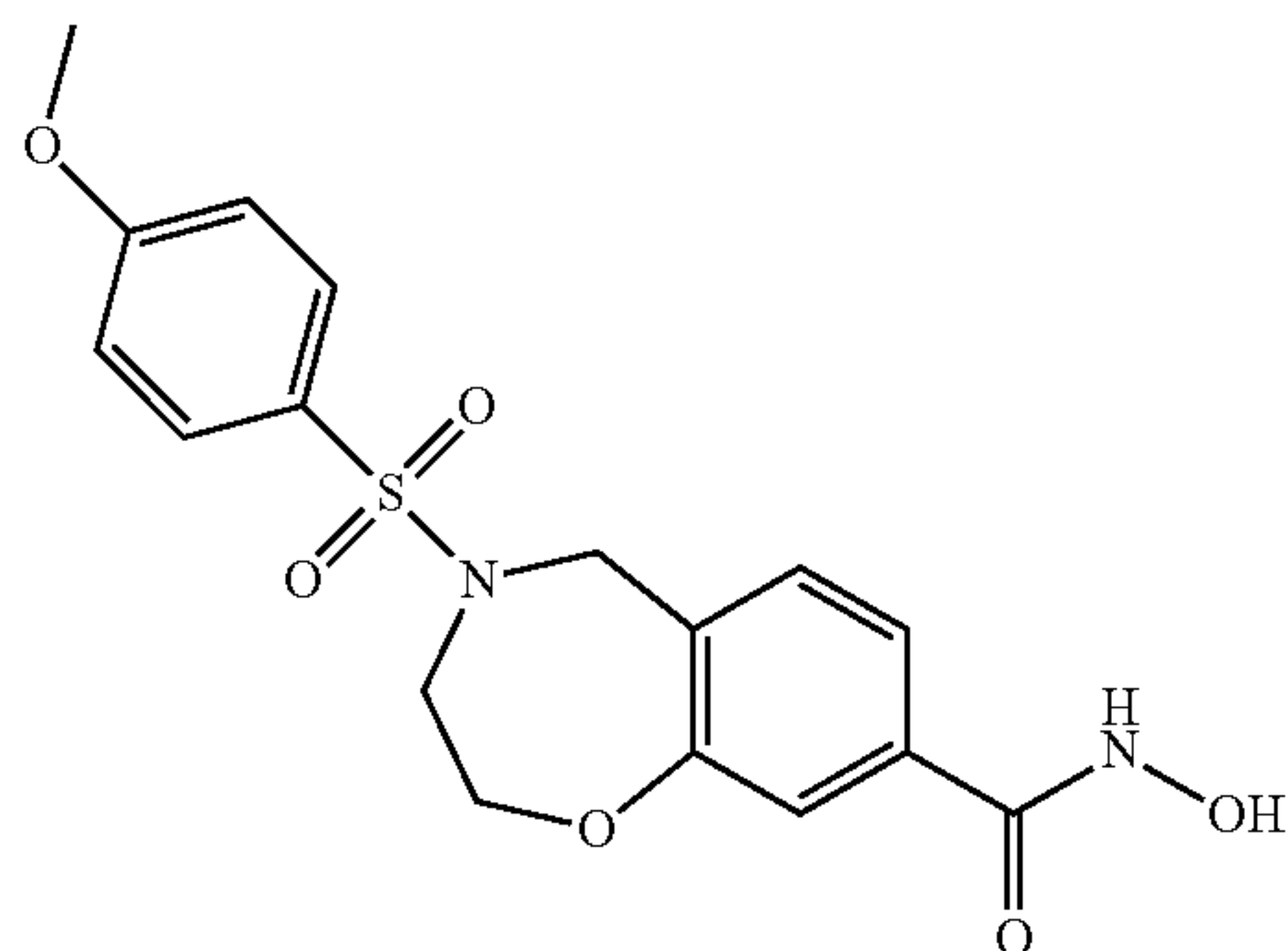
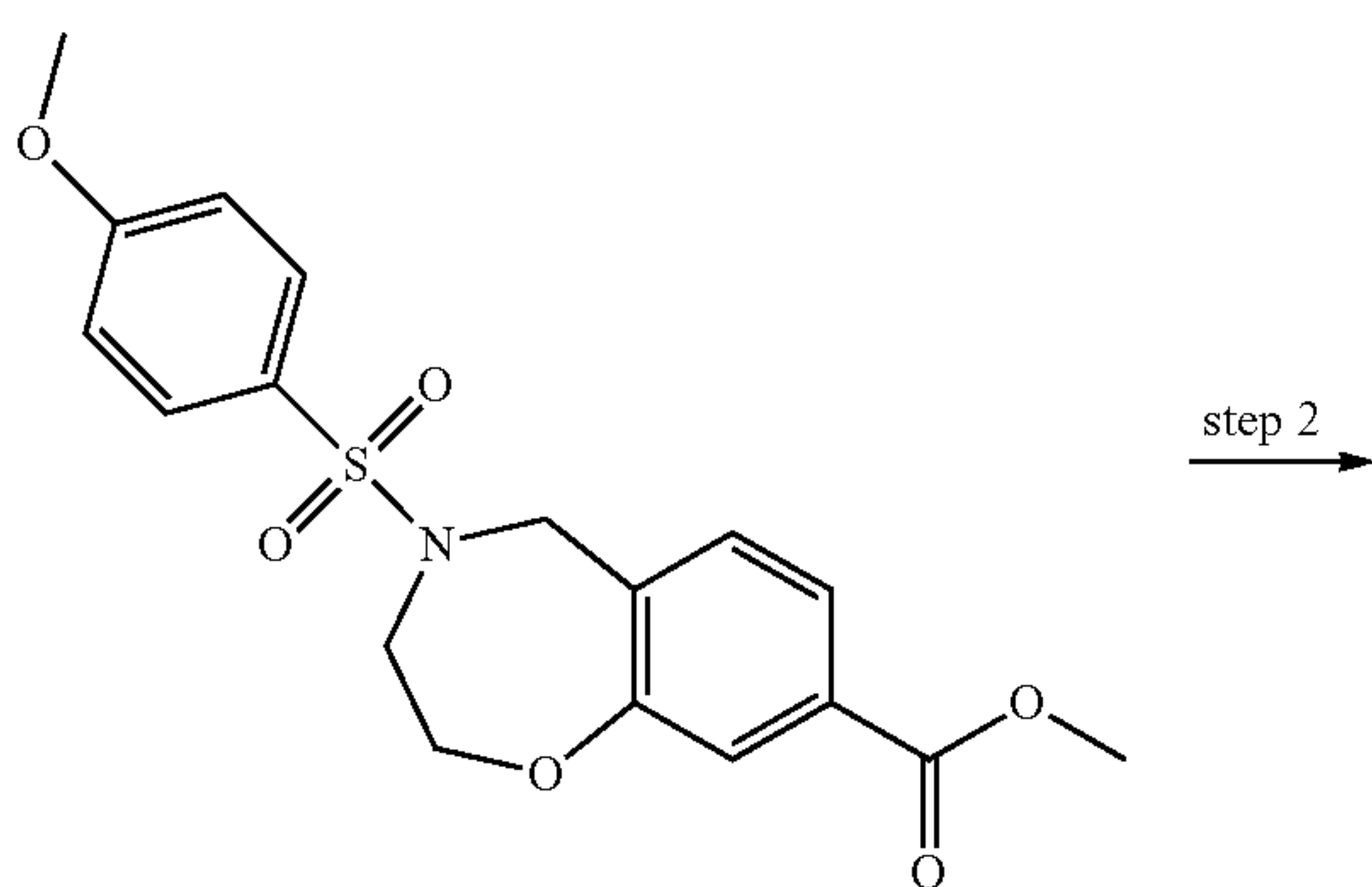
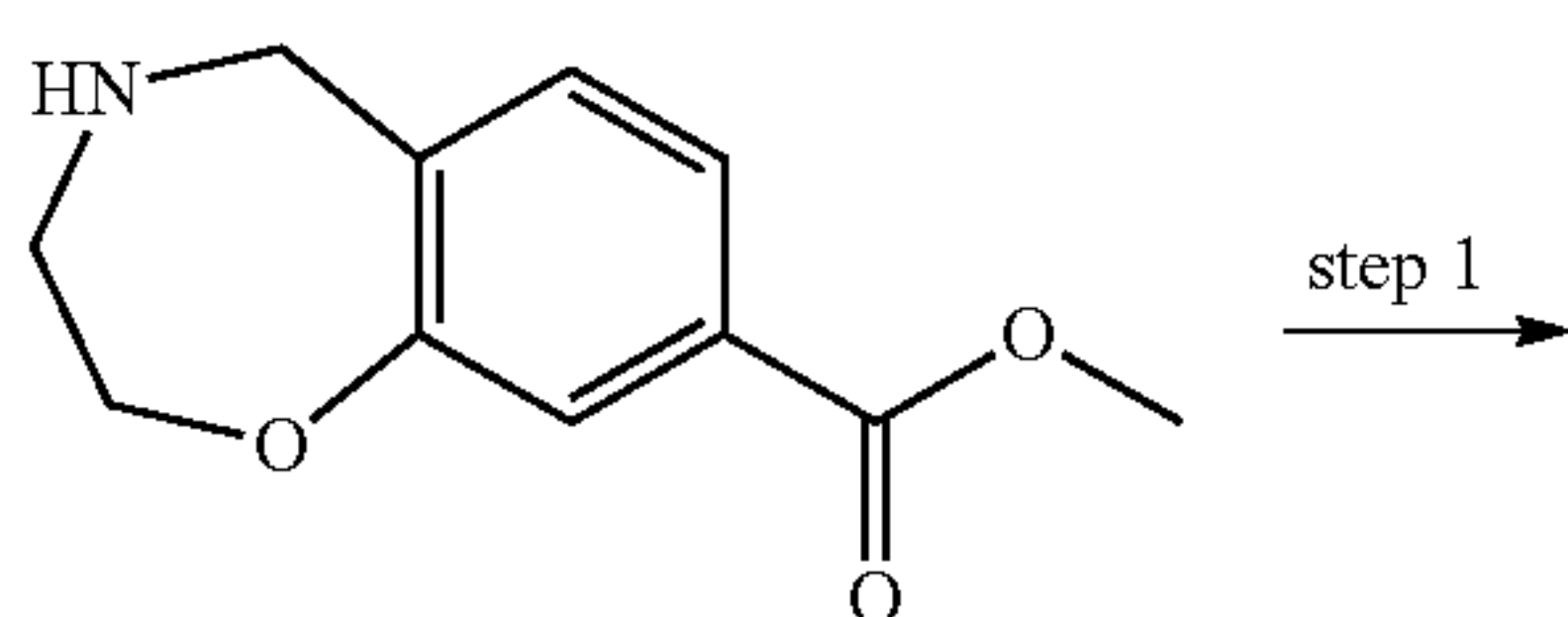
**231**

TABLE 36-continued

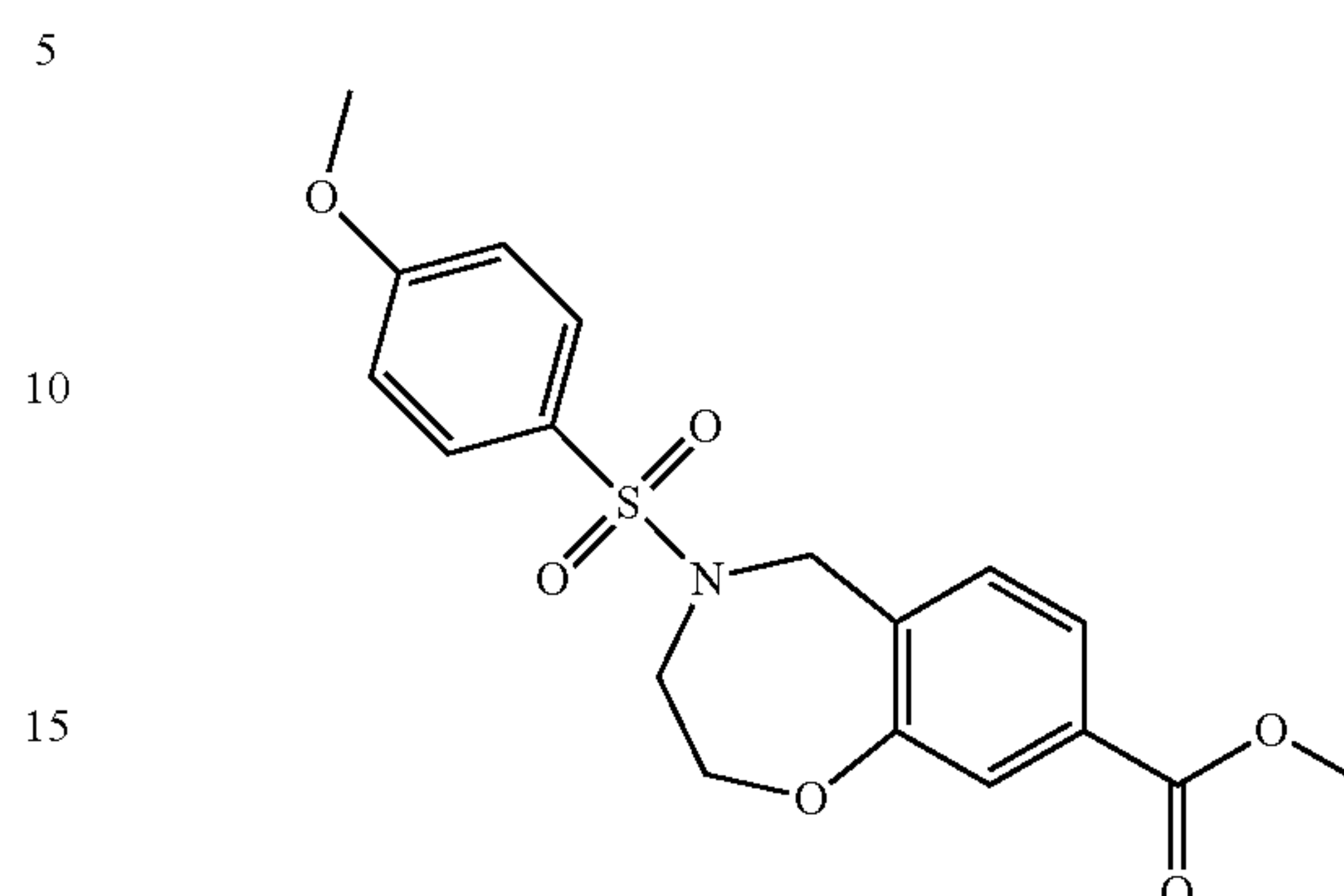
The following compound was prepared by the parallel synthesis method of Example 80.	
Structure	Found M + H (ES)
	342

Example 81

Preparation of N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

**232**

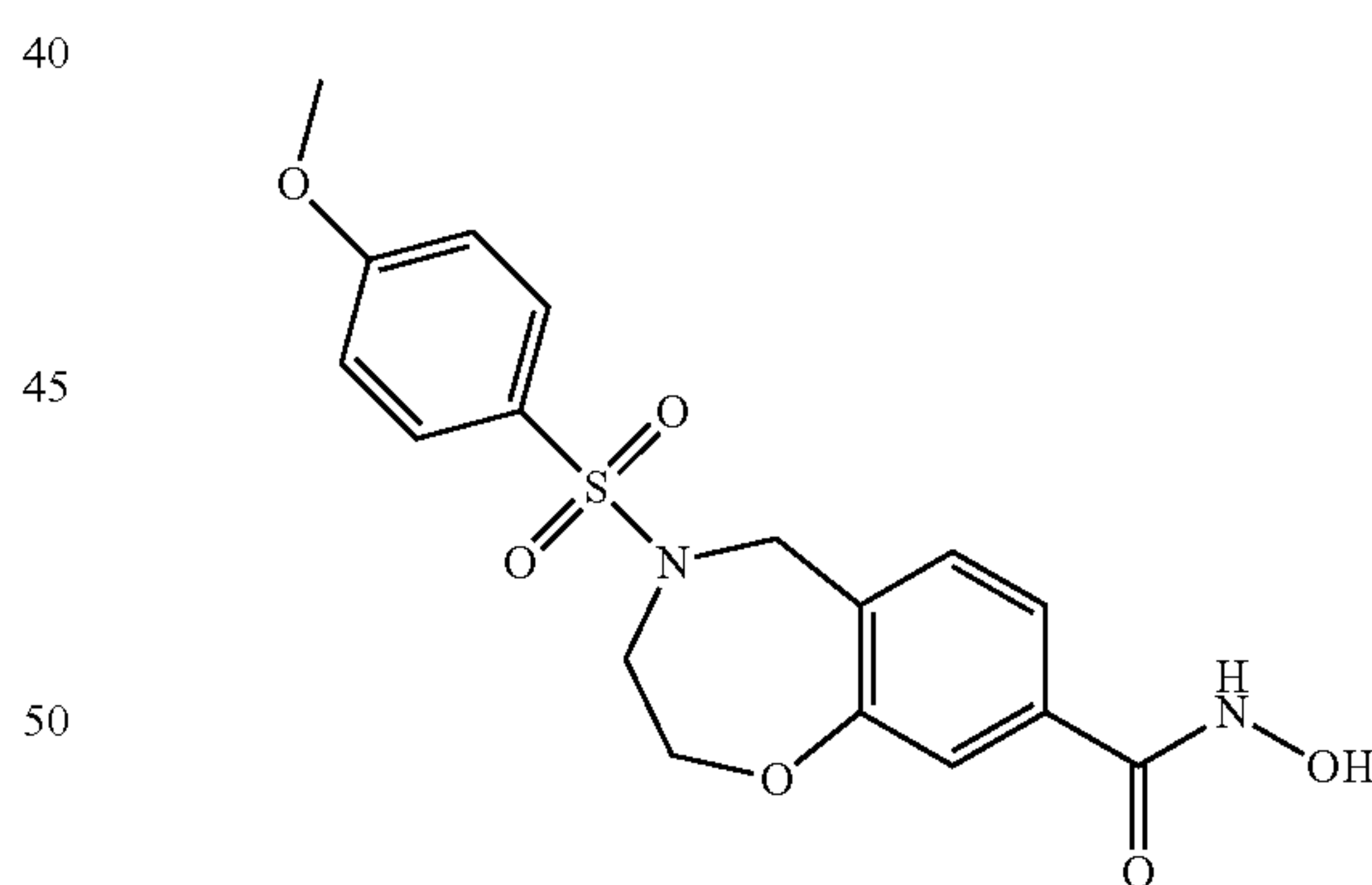
Step-1: Methyl 4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



20

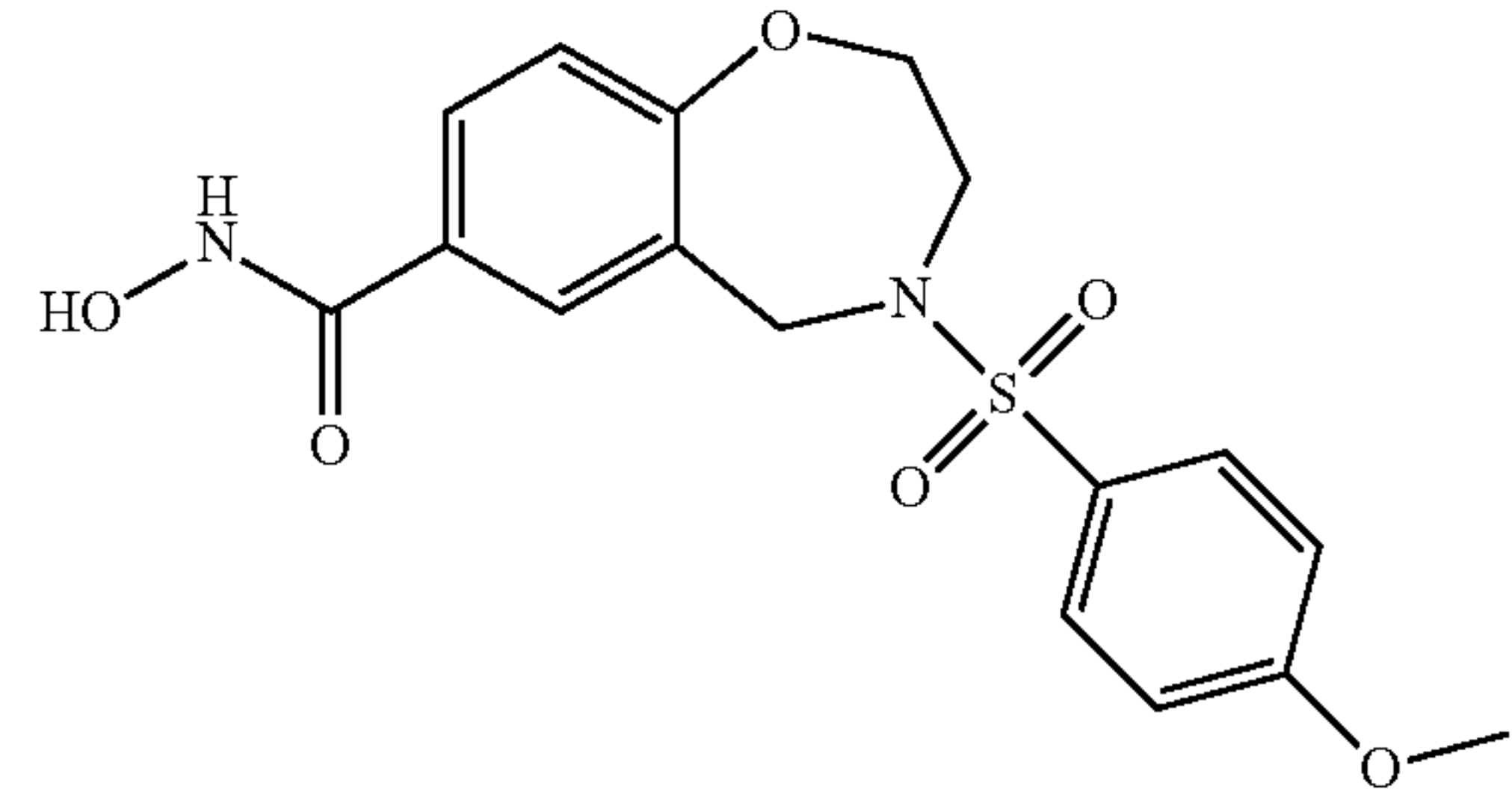
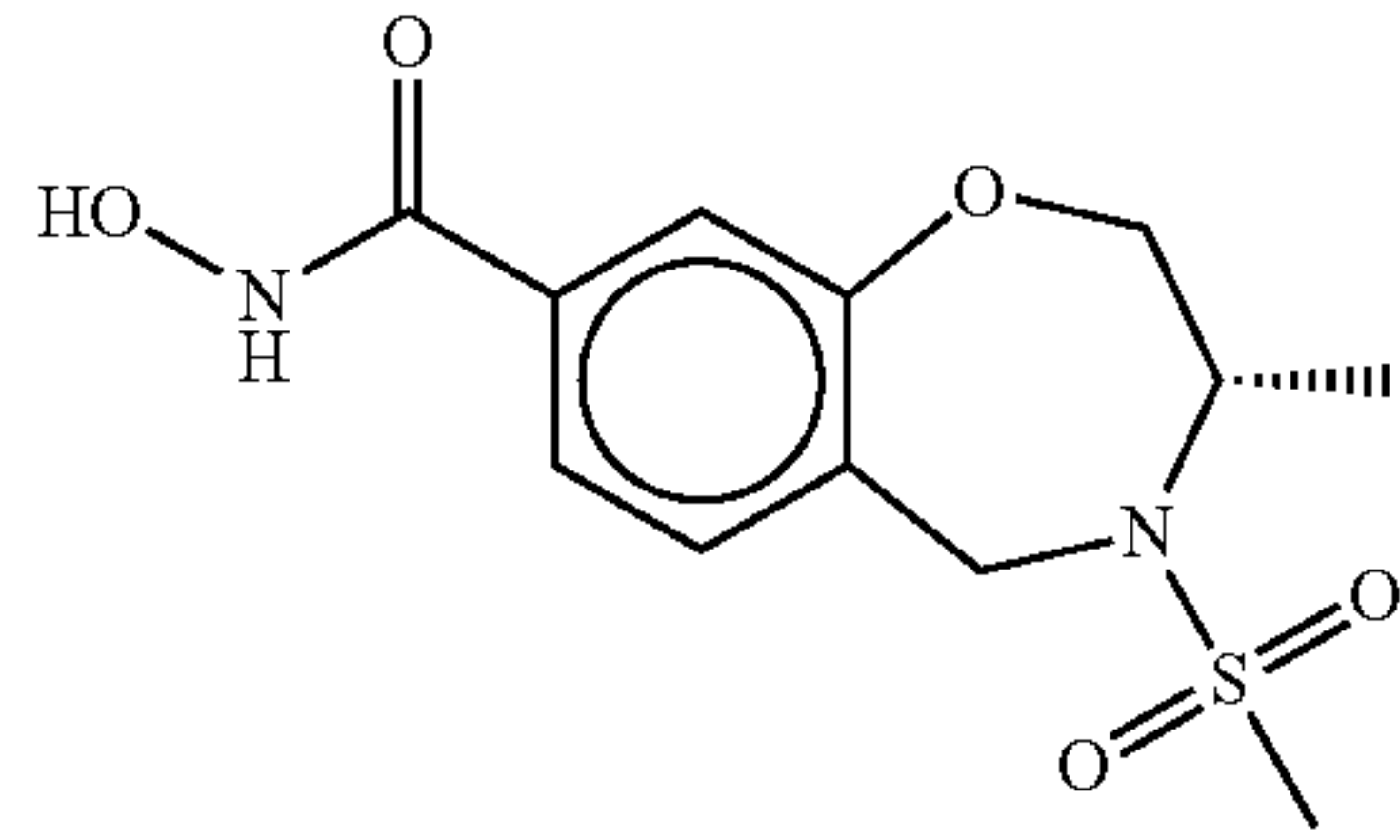
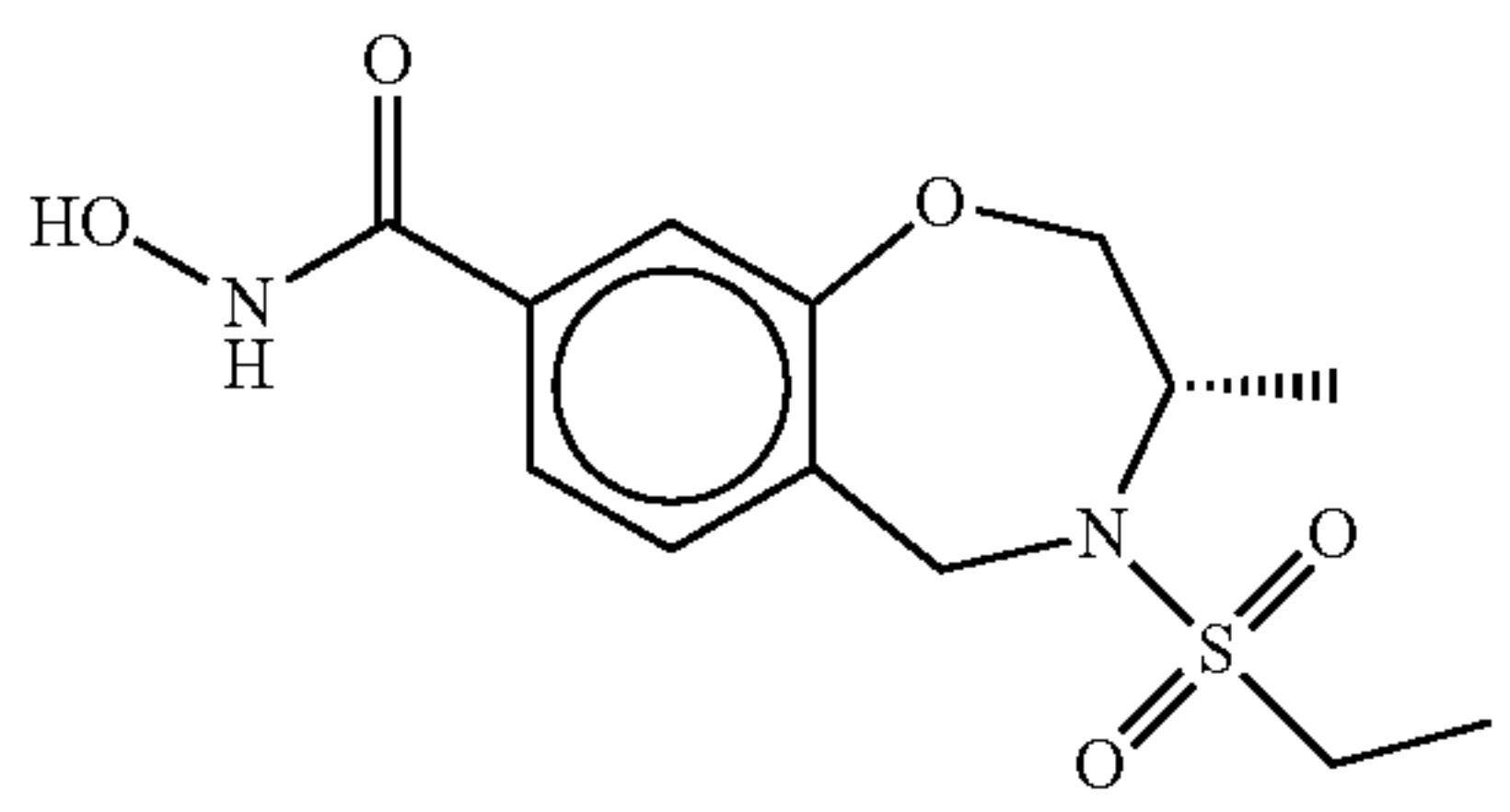
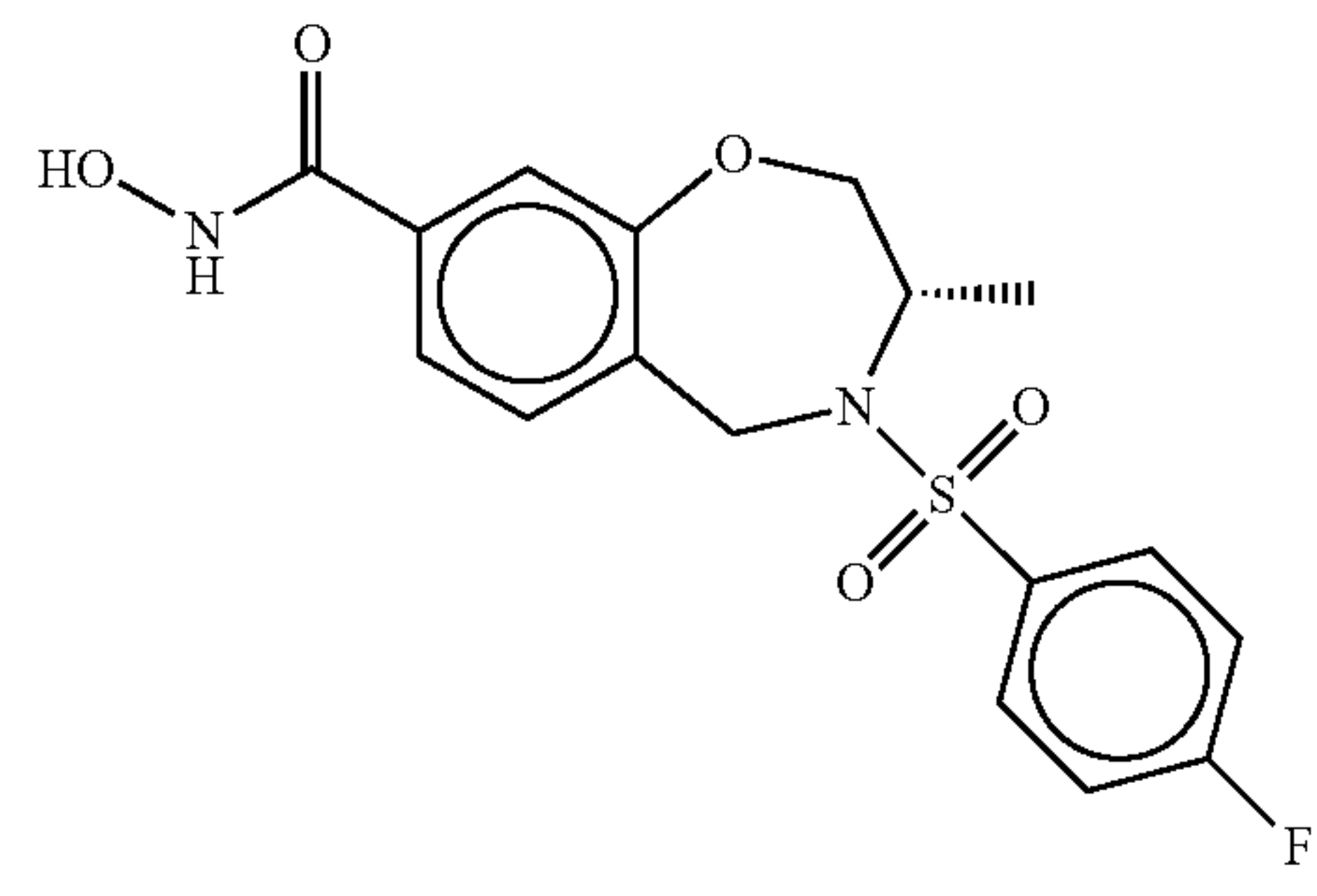
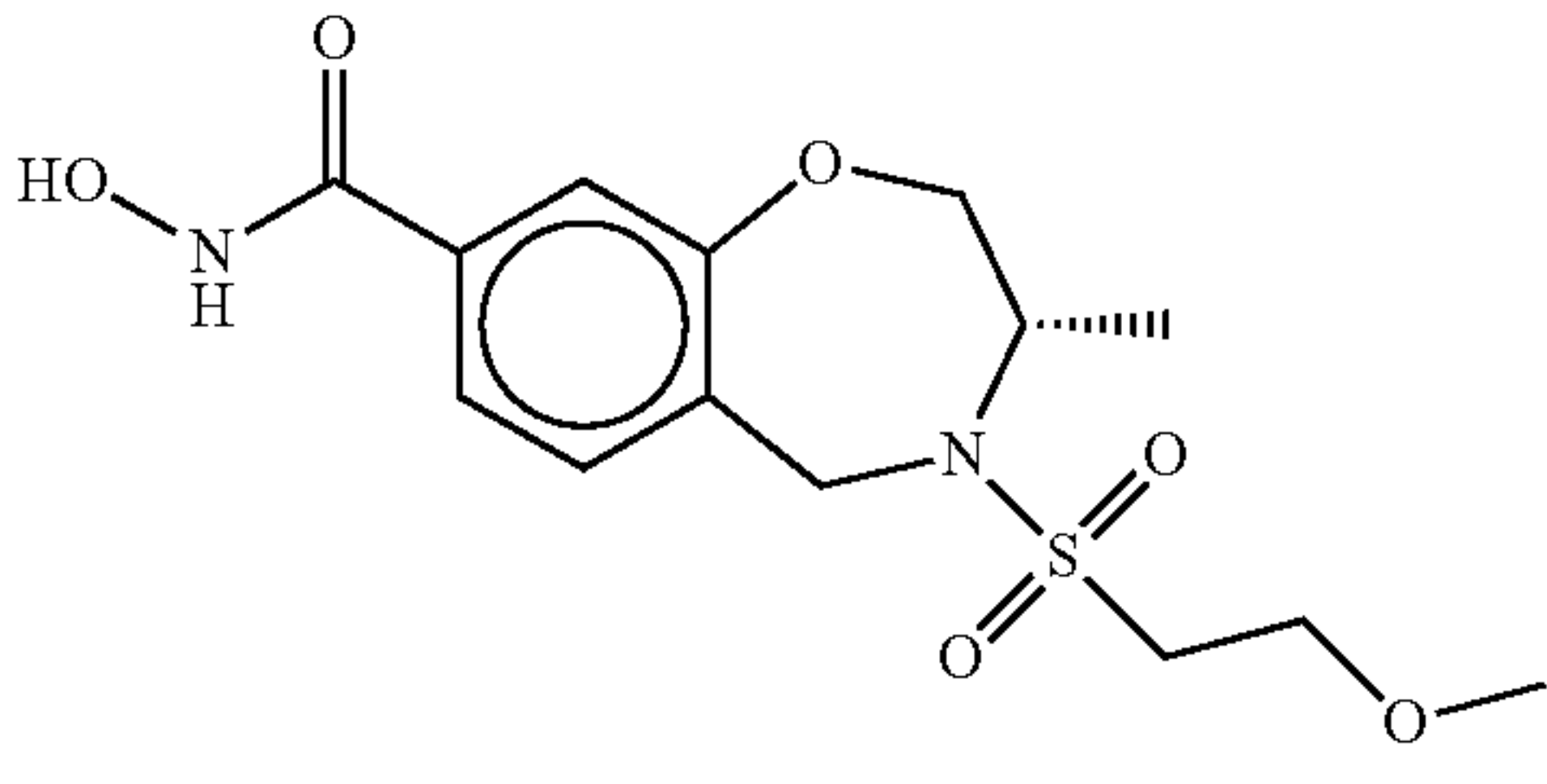
A 2 mL reaction vial was charged with methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (0.2 M in 1,2-dichloroethane, 150  $\mu$ L, 30  $\mu$ mol) and Et<sub>3</sub>N (neat, 10  $\mu$ L, 71  $\mu$ mol). 4-Methoxybenzenesulfonyl chloride (0.2 M in 1,2-dichloroethane, 195  $\mu$ L, 39  $\mu$ mol) was added and the vial was sealed and shaken at room temperature overnight. The reaction mixture was diluted with brine (500  $\mu$ L) and extracted with EtOAc (2 $\times$ 500  $\mu$ L). The combined organic layers were evaporated to dryness under reduced pressure.

Step-2: N-Hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Mixed solvent of THF/MeOH (3:1, 180  $\mu$ L) was added to the vial containing methyl 4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate and it was shaken at 50° C. for 15 min to dissolve the residue. NH<sub>2</sub>OH (50% in water, 125  $\mu$ L) was added followed by aq. 1N NaOH (85  $\mu$ L) and the vial was sealed and shaken at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in DMSO (500  $\mu$ L) then purified by HPLC to afford the title compound (9.1 mg, 80% yield). MS: (ES, m/z): 379 [M+H]<sup>+</sup>.

TABLE 37

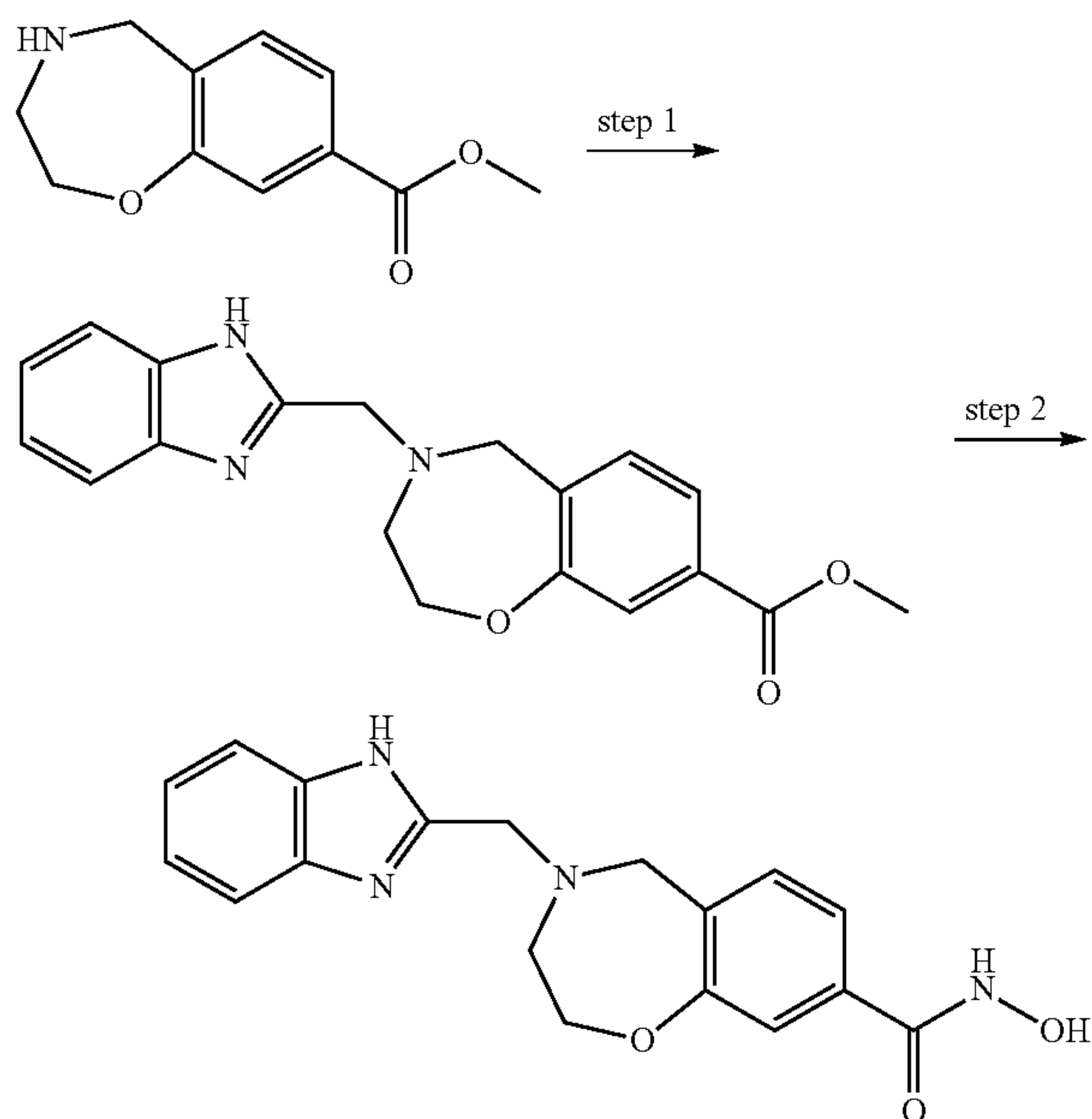
The following compound was prepared by the parallel synthesis method of Example 81.			
Structure	Found M + H (ES)	Structure	Found M + H (ES)
	379		301
	315		381
	345		



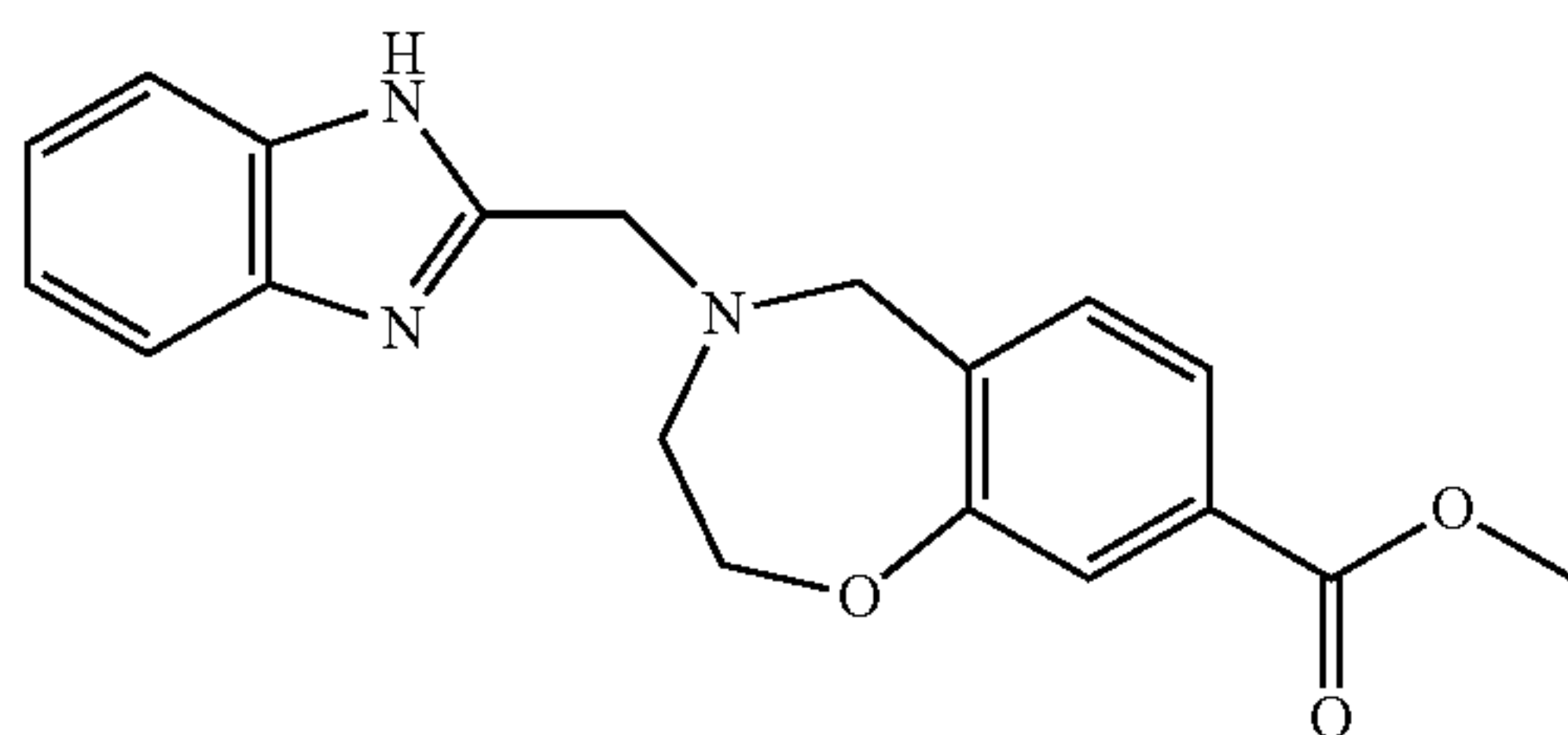
**235**

## Example 82

Preparation of 4-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

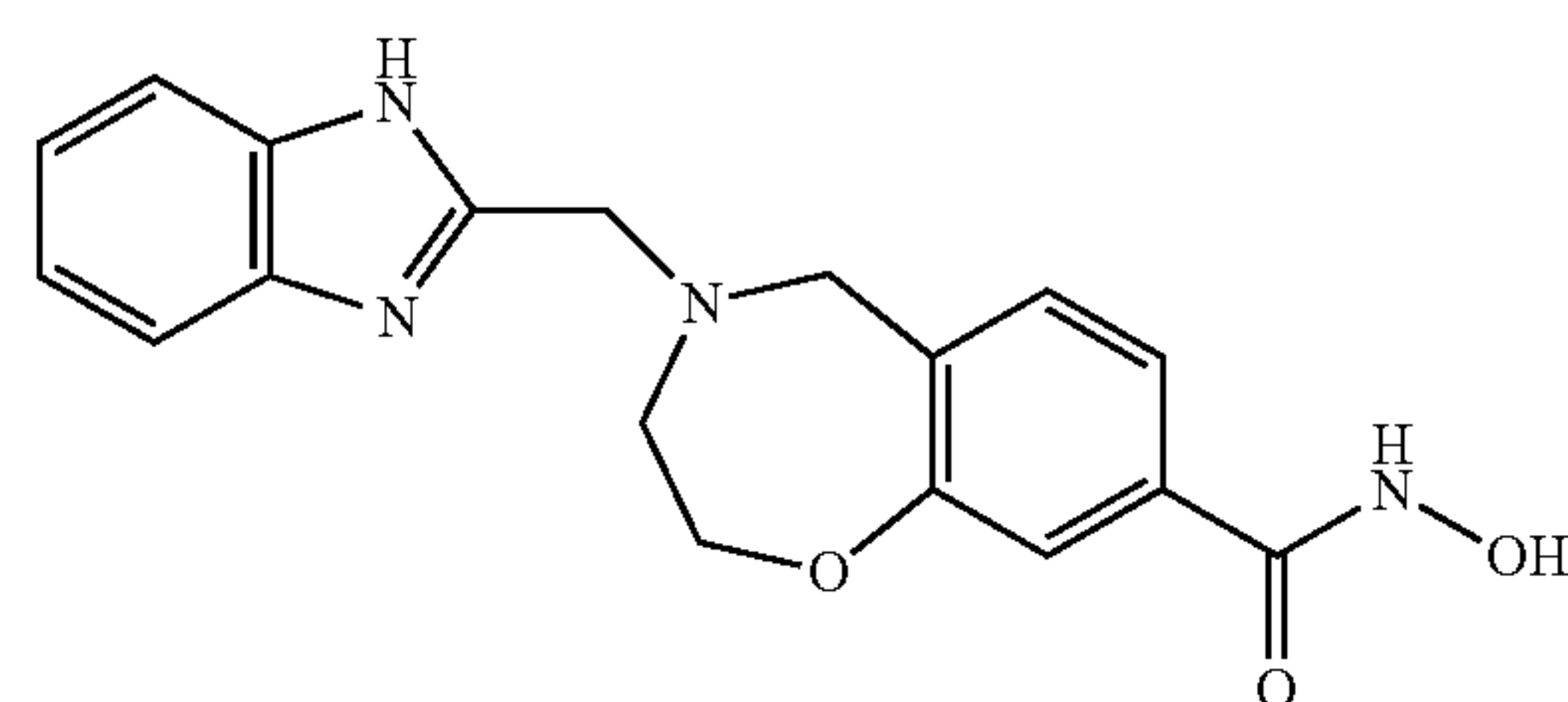


Step-1: Methyl 4-((1H-benzo[d]imidazol-2-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

**236**

A 2 mL reaction vial was charged with methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (0.2M in N,N-dimethylacetamide, 200  $\mu$ L, 40  $\mu$ mol) and 2-(chloromethyl)-1H-benzo[d]imidazole (0.2M in N,N-dimethylacetamide, 200  $\mu$ L, 40  $\mu$ mol). Solid  $K_2CO_3$  (22 mg, 160  $\mu$ mol) was added and the vial was sealed and shaken at room temperature overnight. The reaction mixture was diluted with brine (500  $\mu$ L) and extracted with EtOAc (2 $\times$ 500  $\mu$ L). The combined organic layers were evaporated to dryness under reduced pressure.

Step-2: 4-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Mixed solvent of THF/MeOH (3:1, 180  $\mu$ L) was added to the vial containing methyl 4-((1H-benzo[d]imidazol-2-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate and it was shaken at 50° C. for 15 min to dissolve the residue.  $NH_2OH$  (50% in water, 125  $\mu$ L) was added followed by aq. 1N NaOH (75  $\mu$ L) and the vial was sealed and shaken at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in DMSO (500  $\mu$ L) then purified by HPLC to afford the title compound (9.8 mg, 72% yield). MS: (ES, m/z): 339  $[M+H]^+$ .

TABLE 38

The following compounds were prepared by the parallel synthesis method of Example 82.

Structure	Found M + H (ES)	Structure	Found M + H (ES)
	339		343

TABLE 38-continued

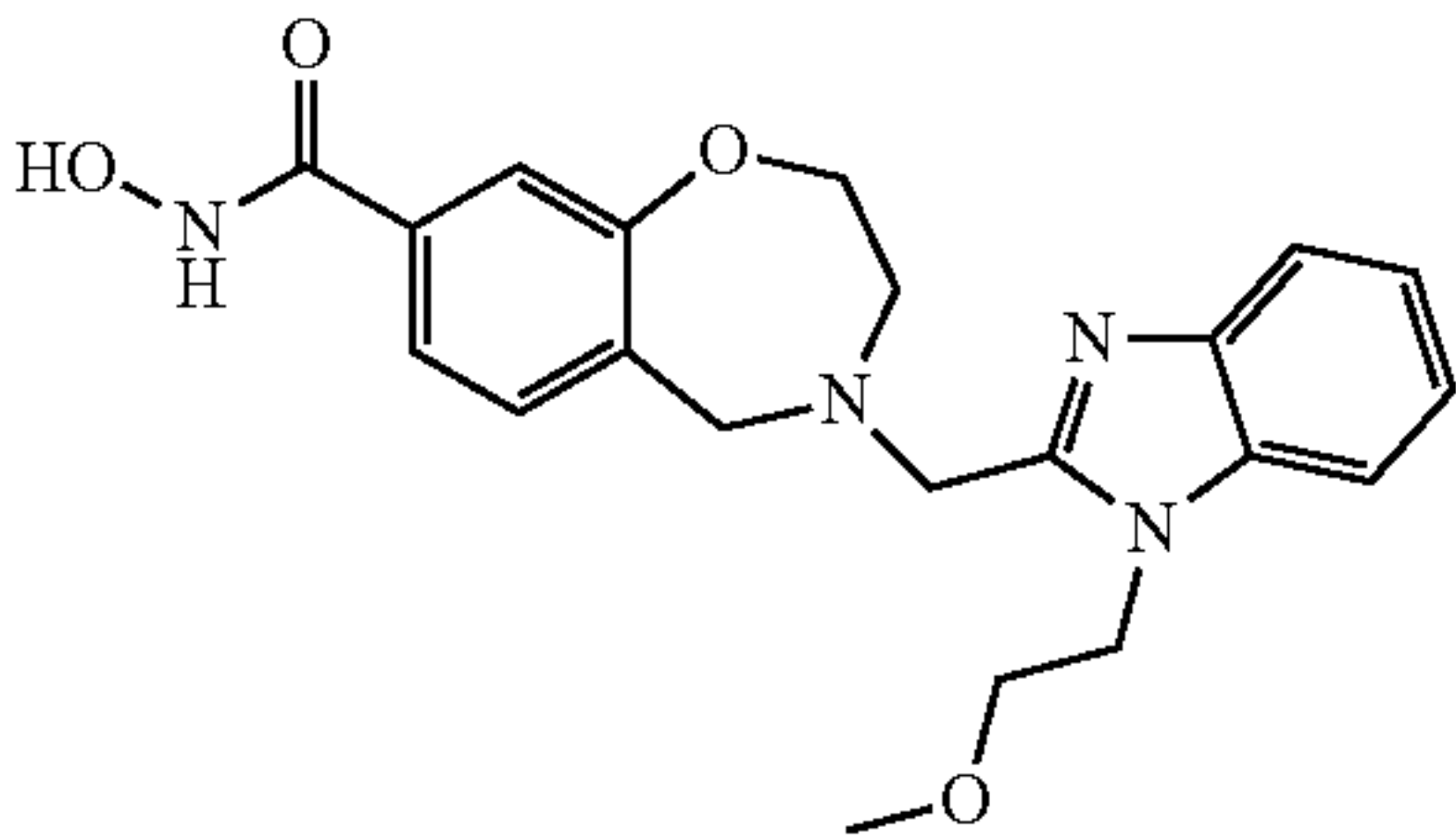
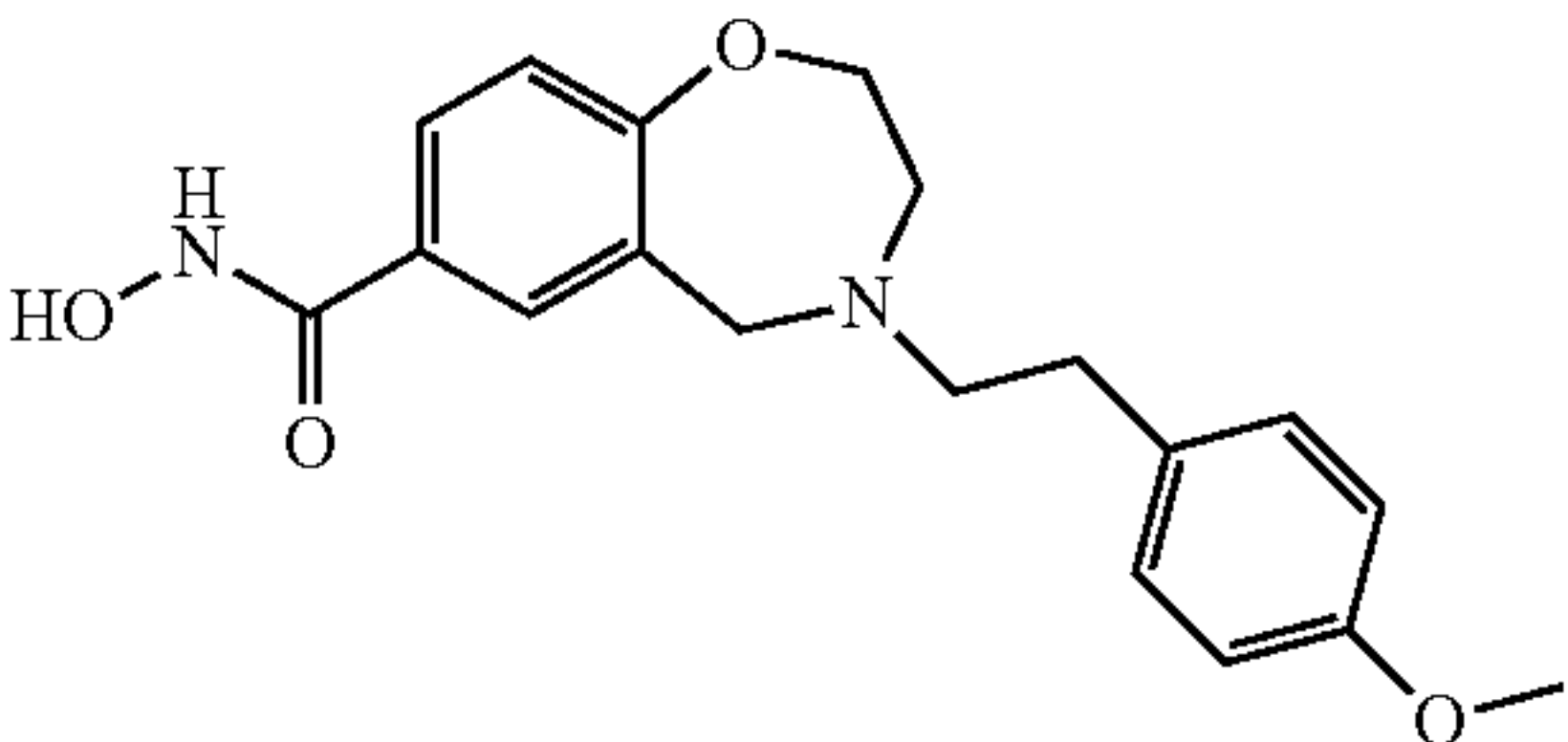
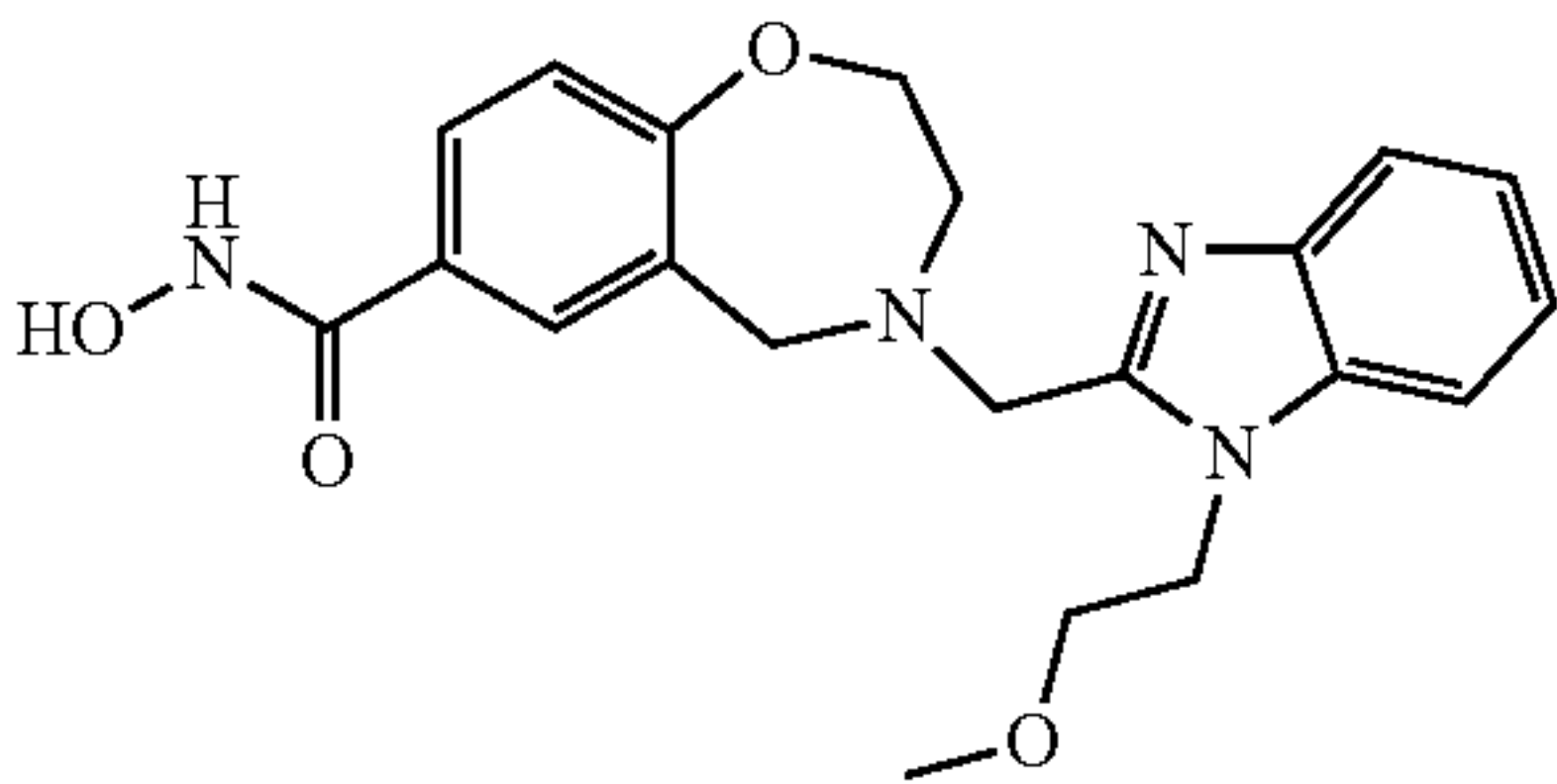
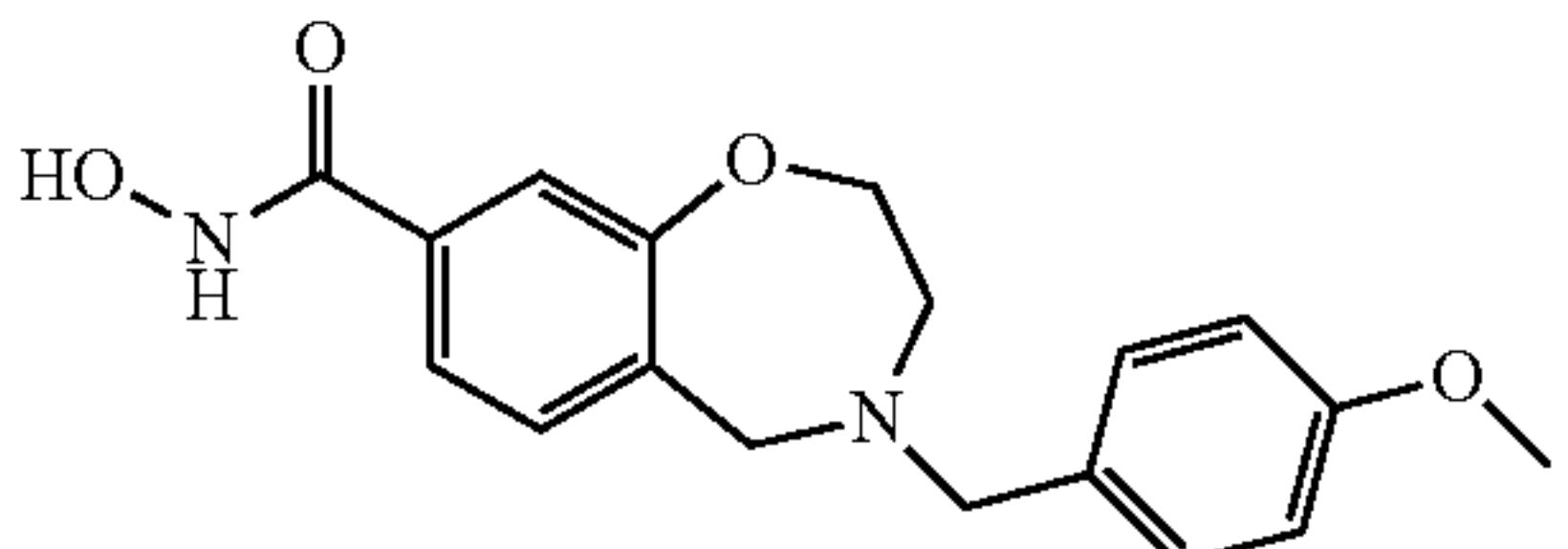
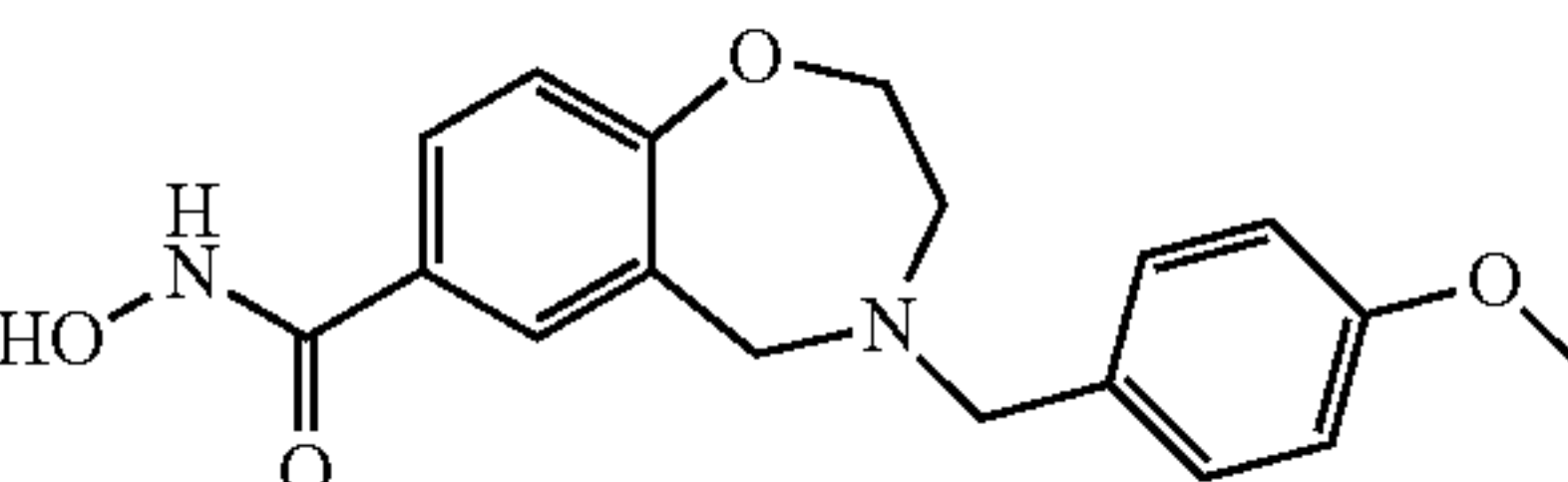
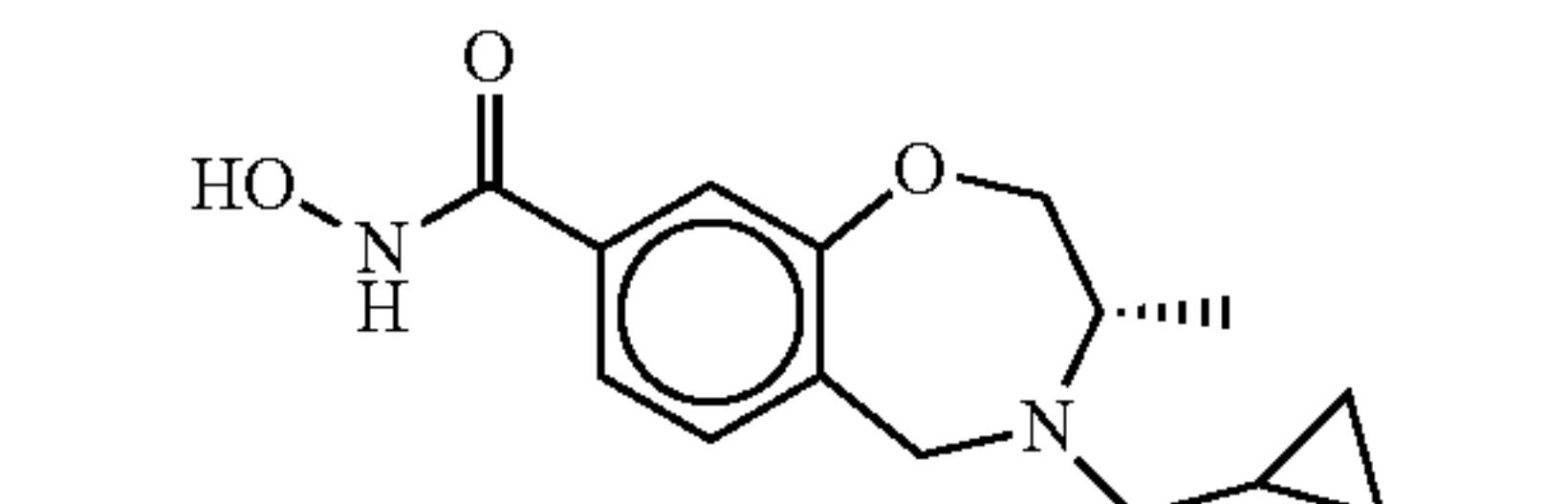
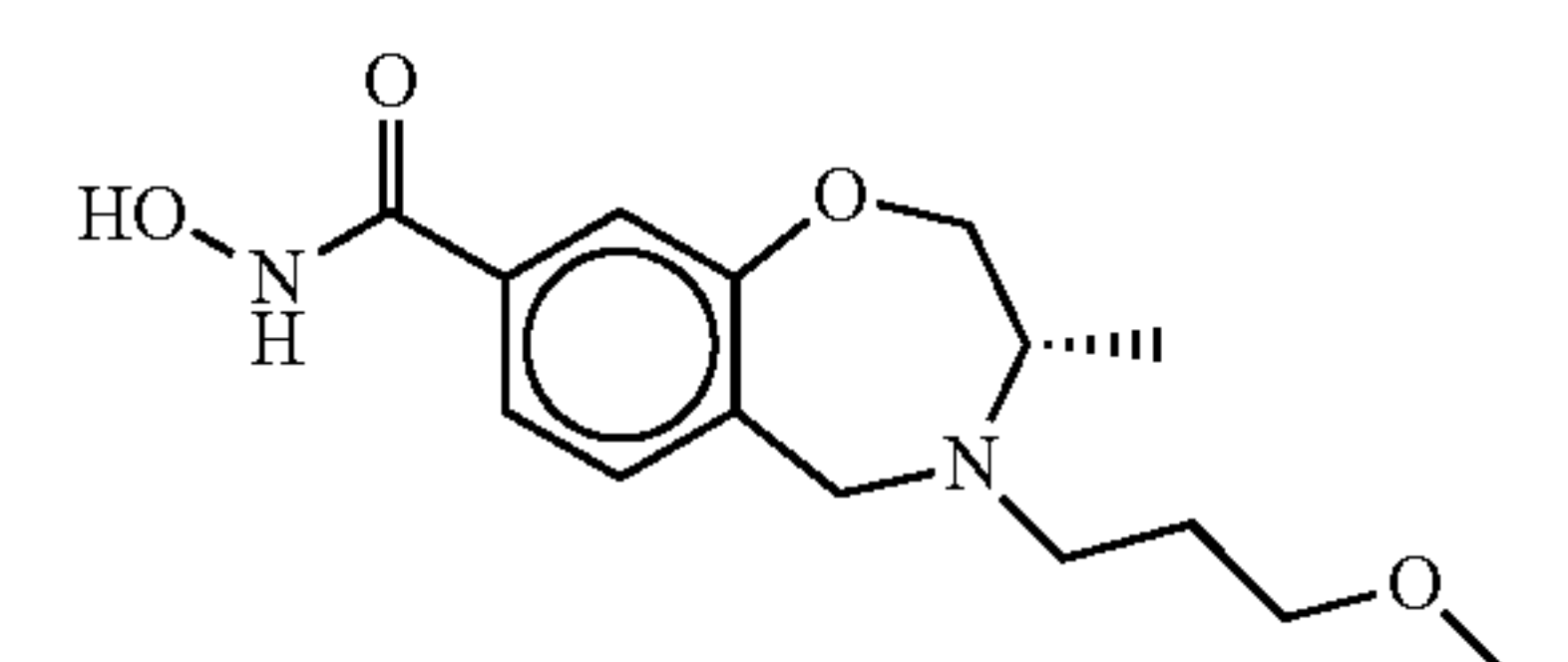
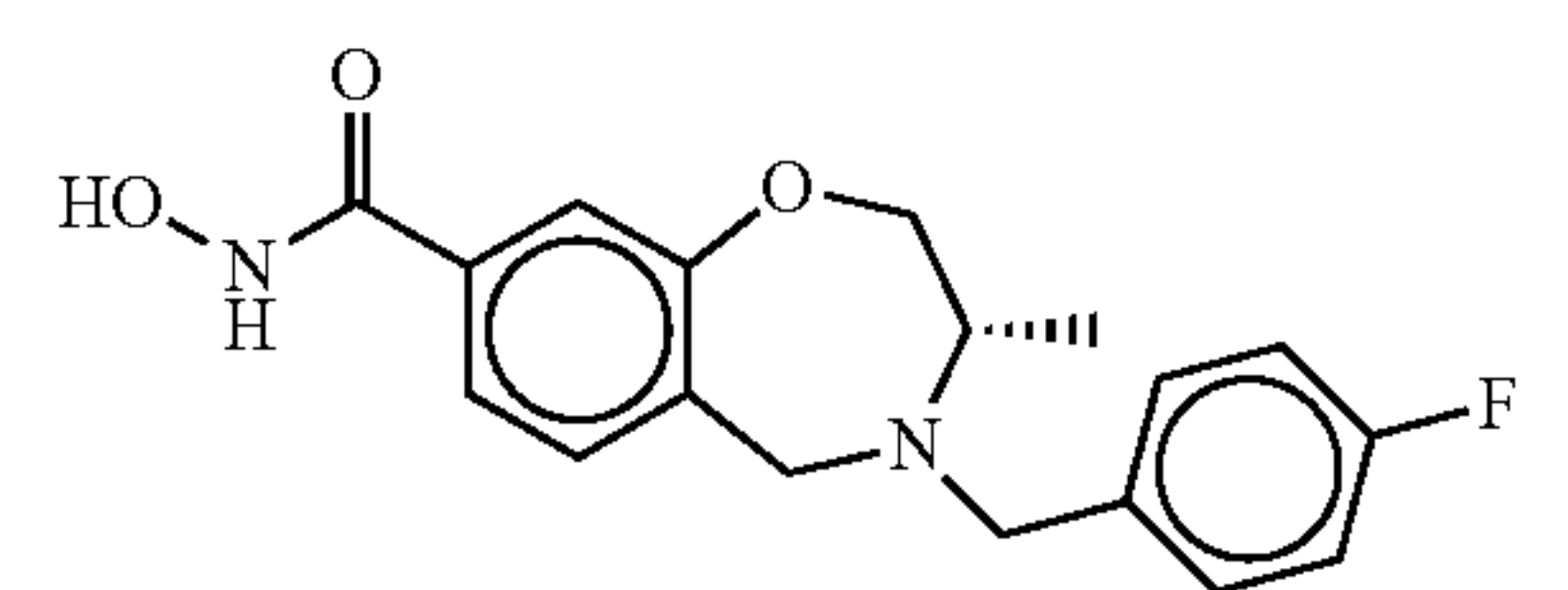
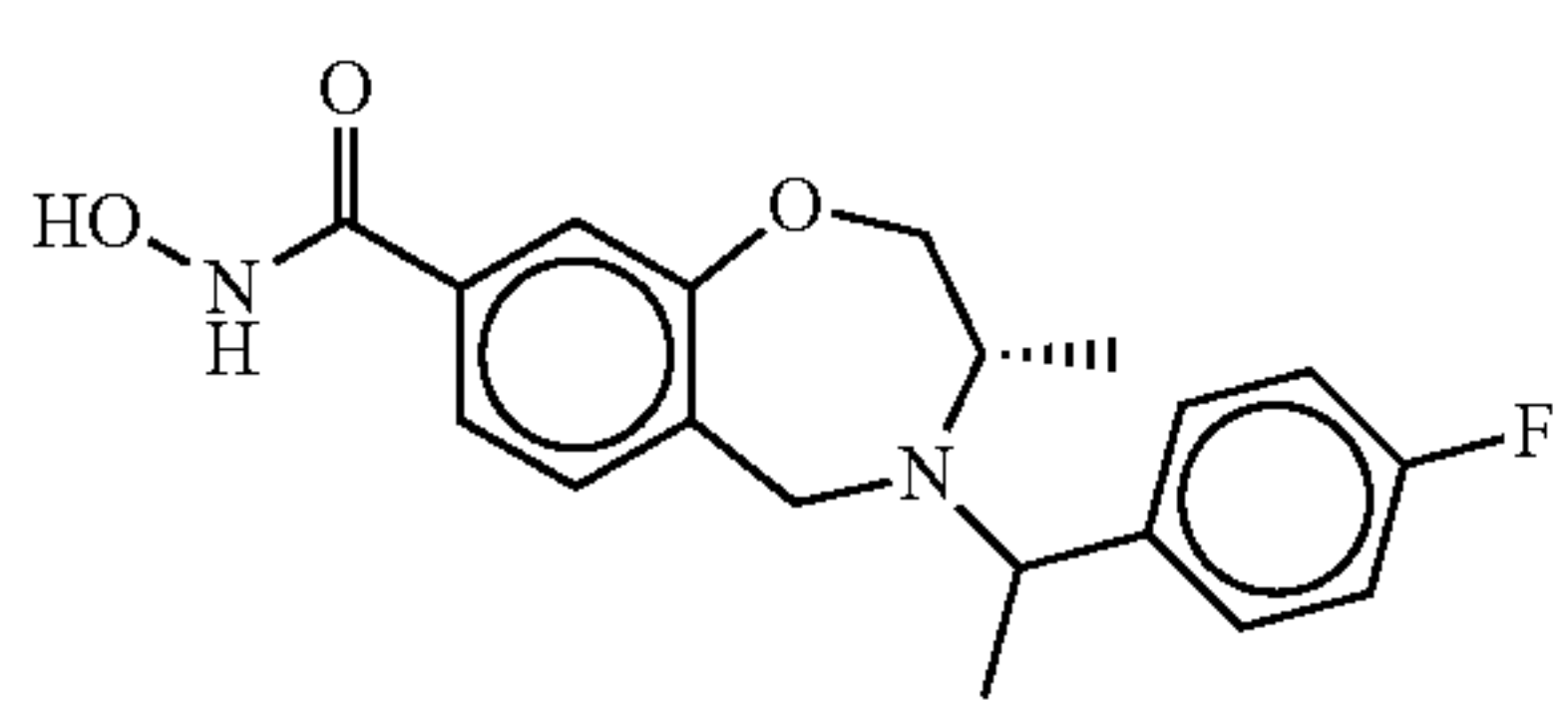
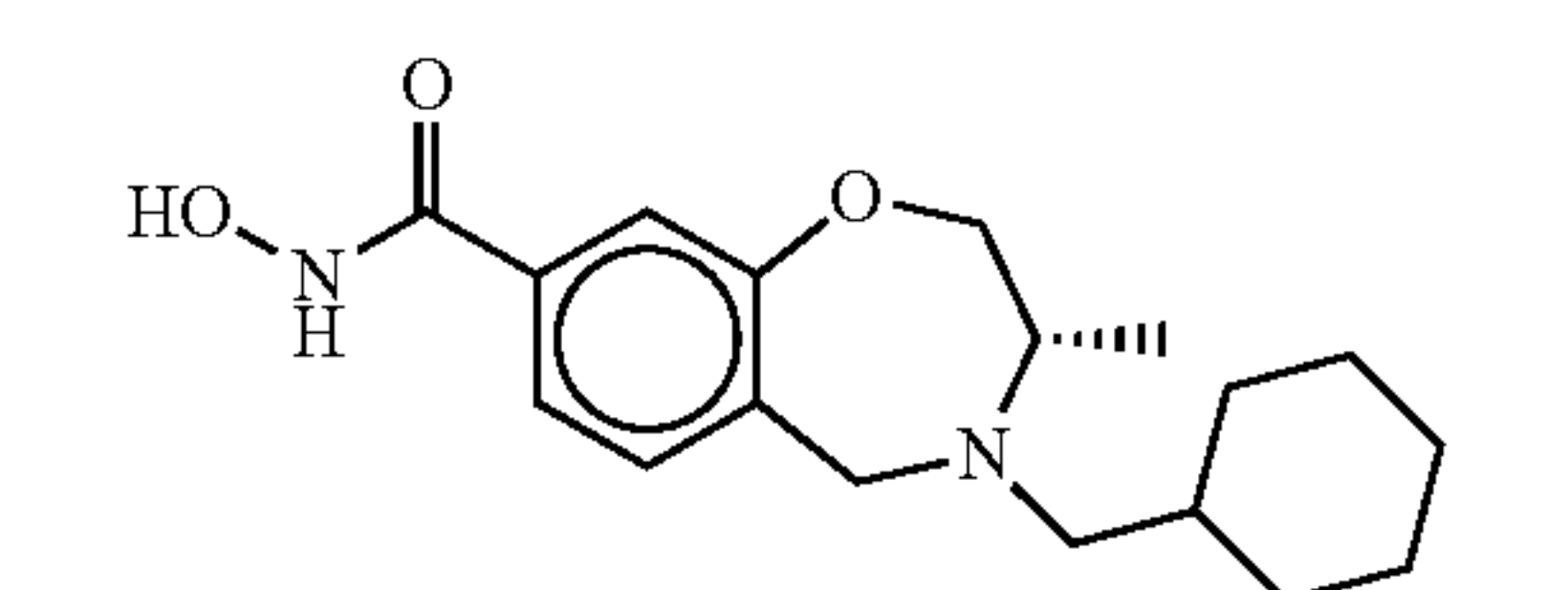
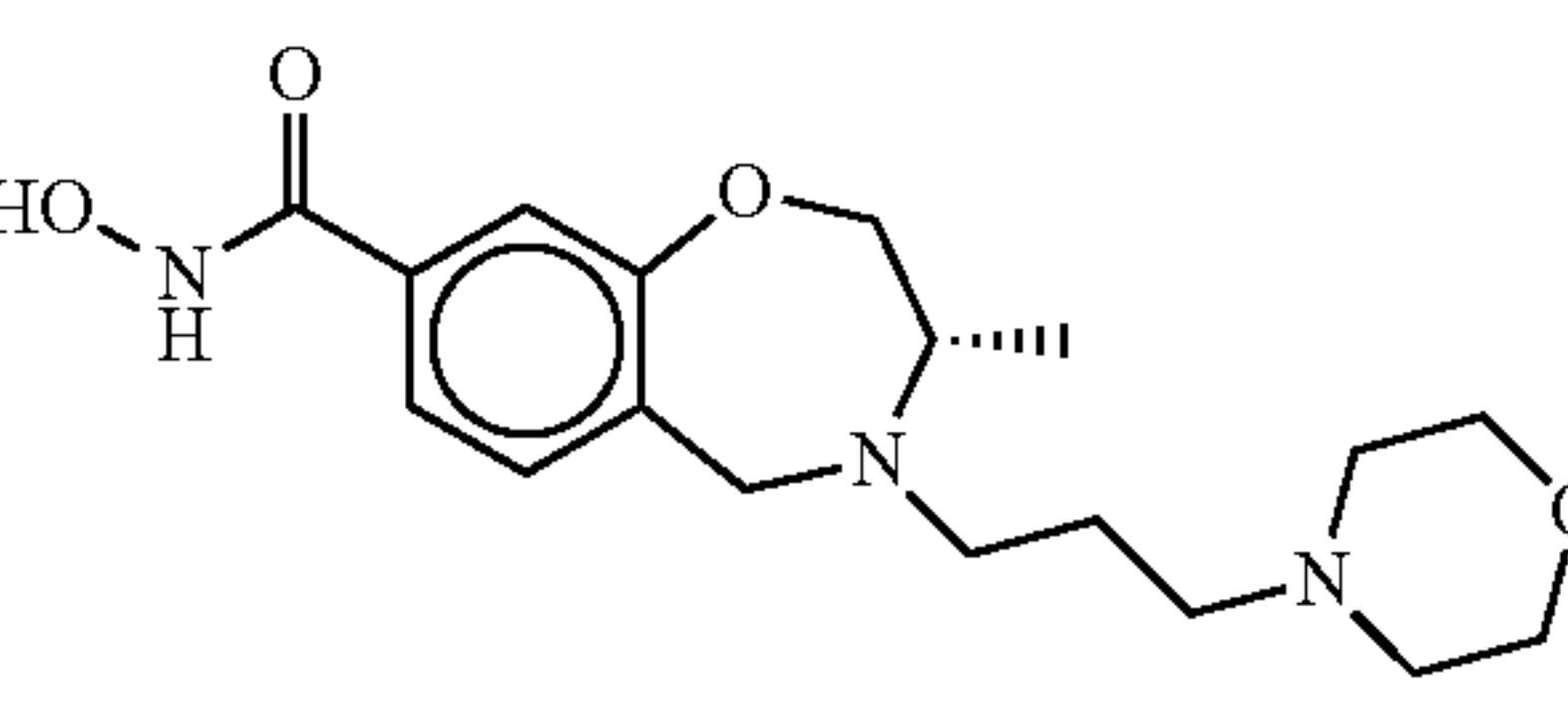
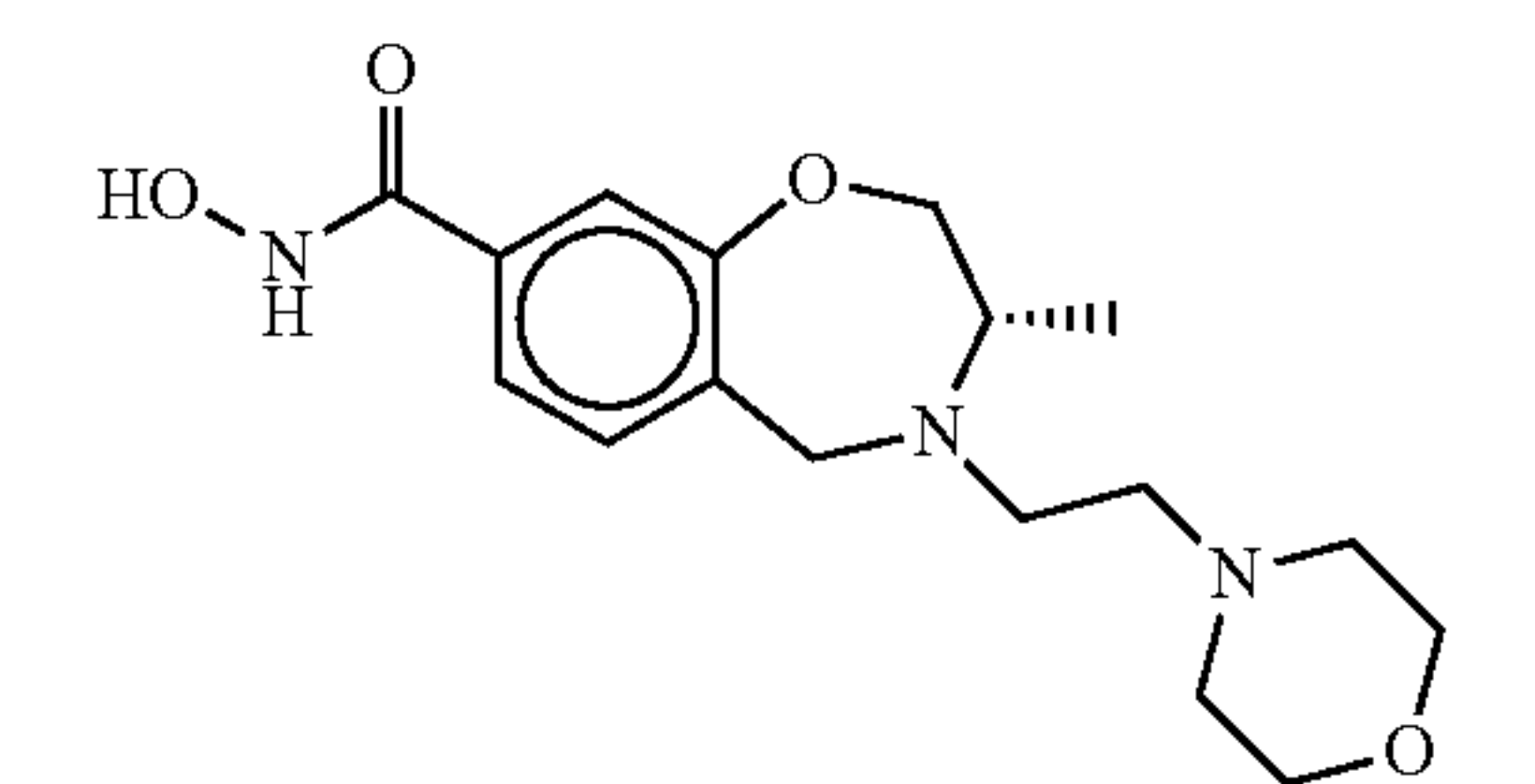
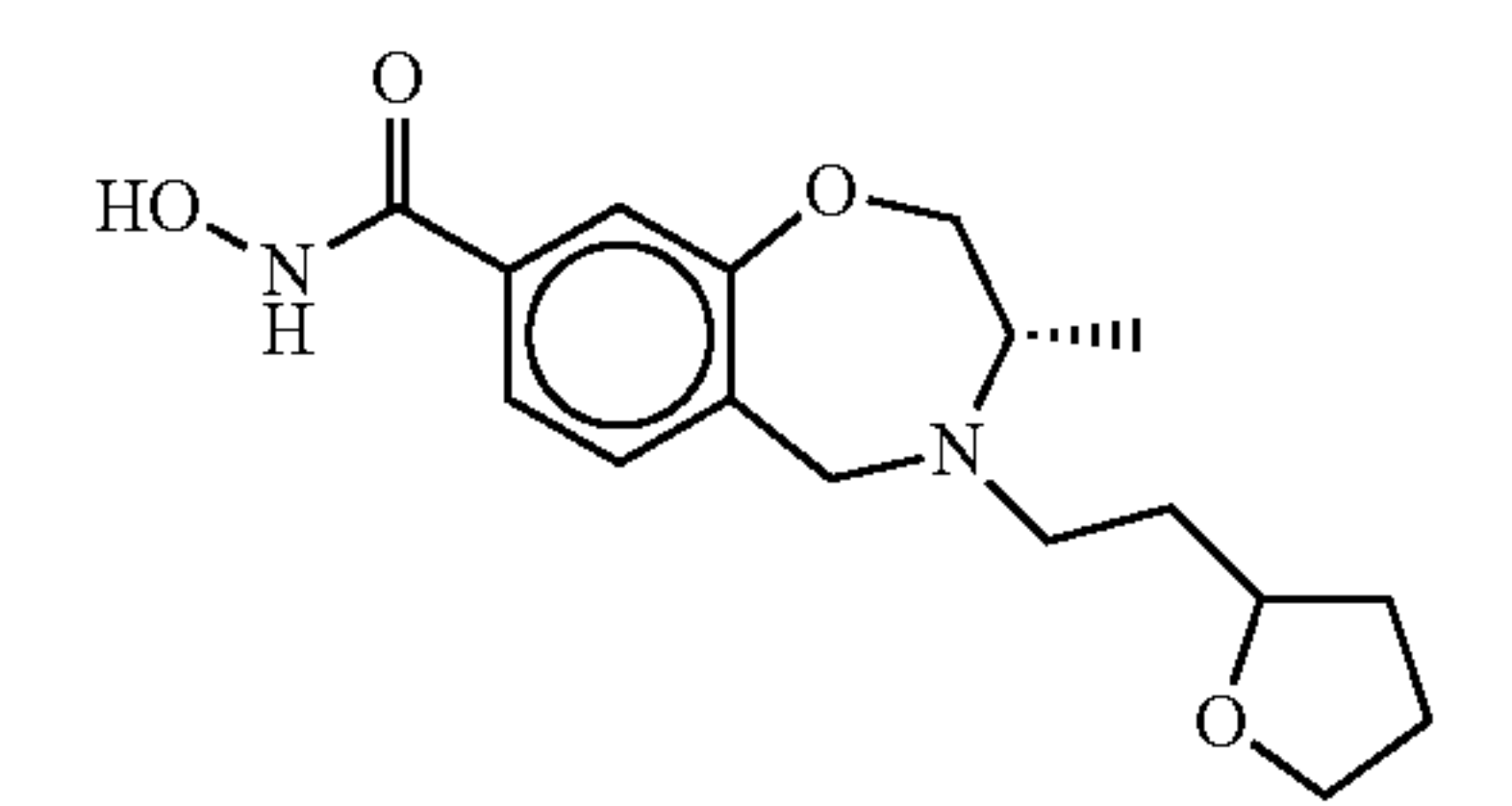
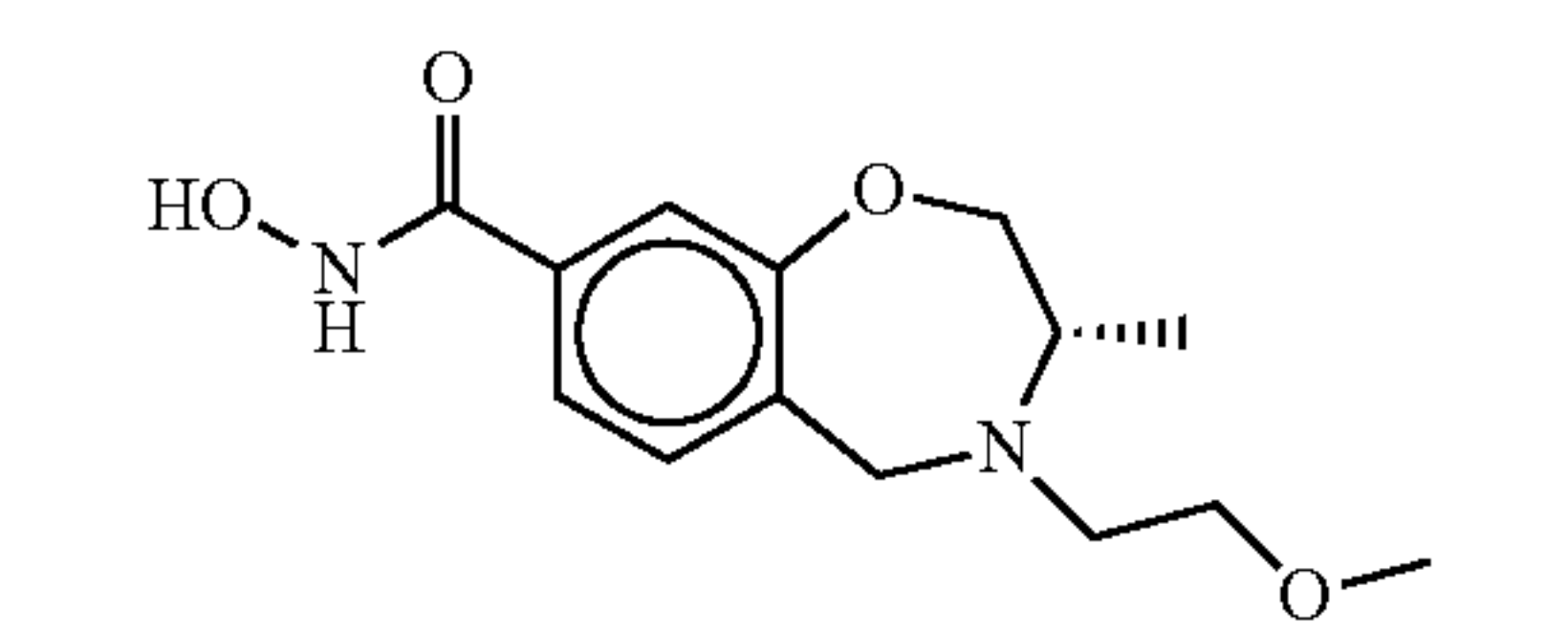
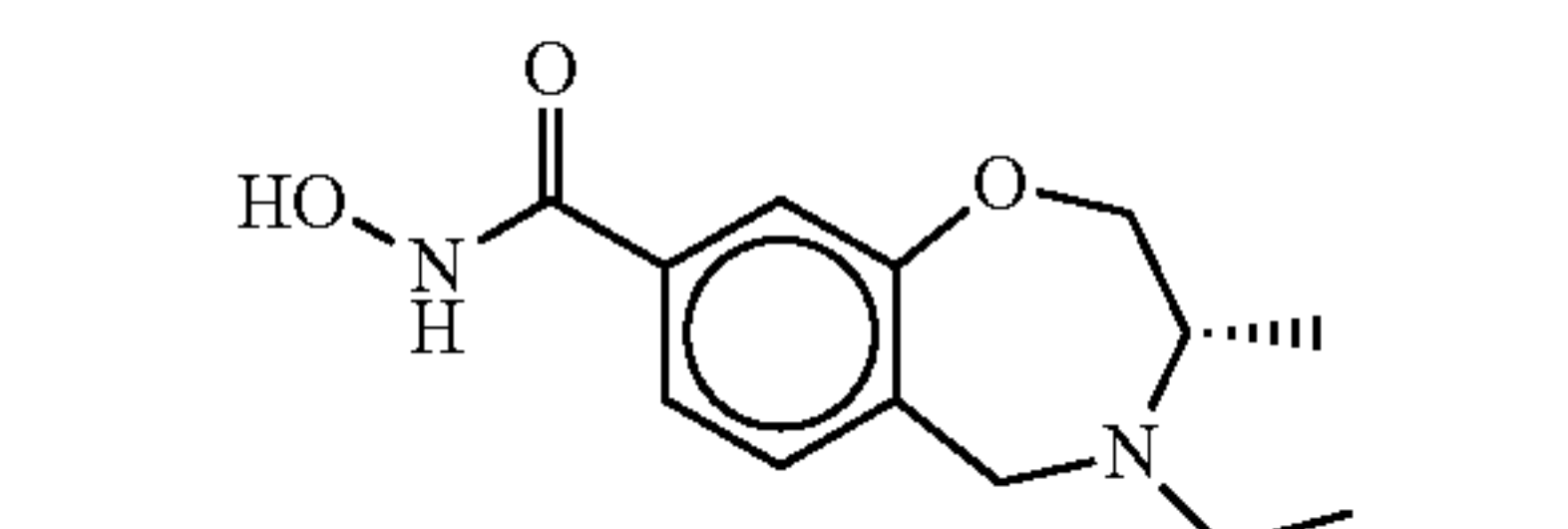
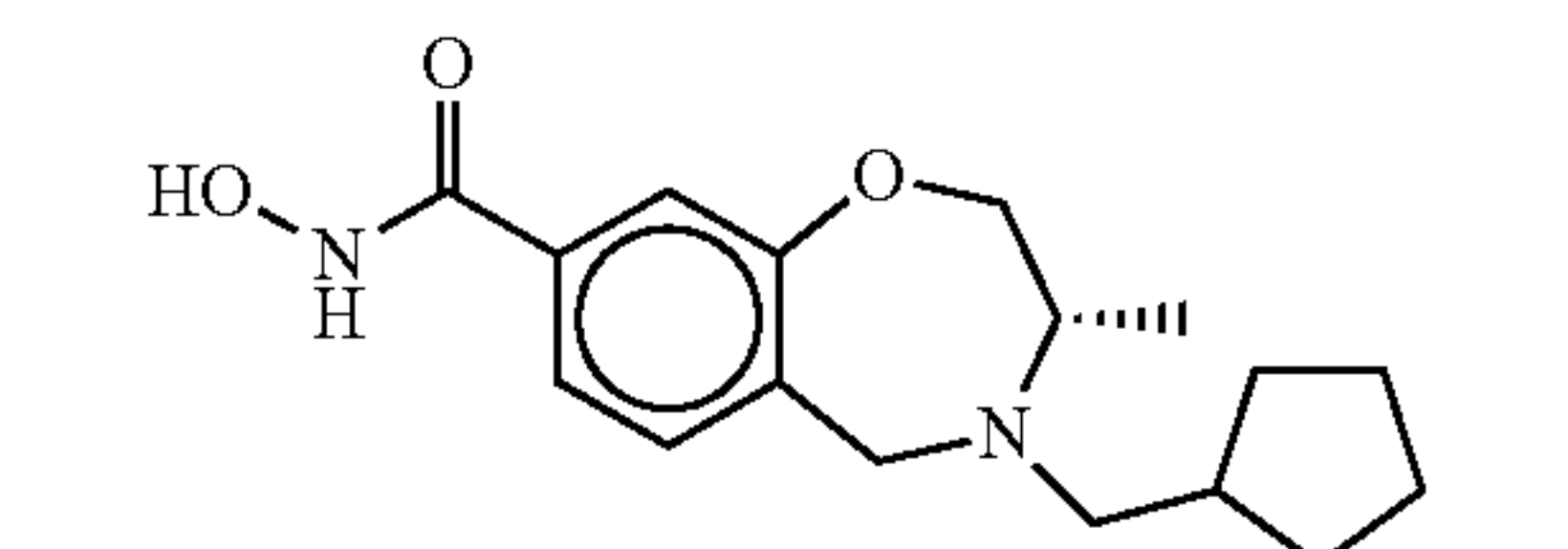
The following compounds were prepared by the parallel synthesis method of Example 82.			
Structure	Found M + H (ES)	Structure	Found M + H (ES)
	397		343
	397		329
	329		277
	295		331
	345		319
	350		336
	321		281
	251		305

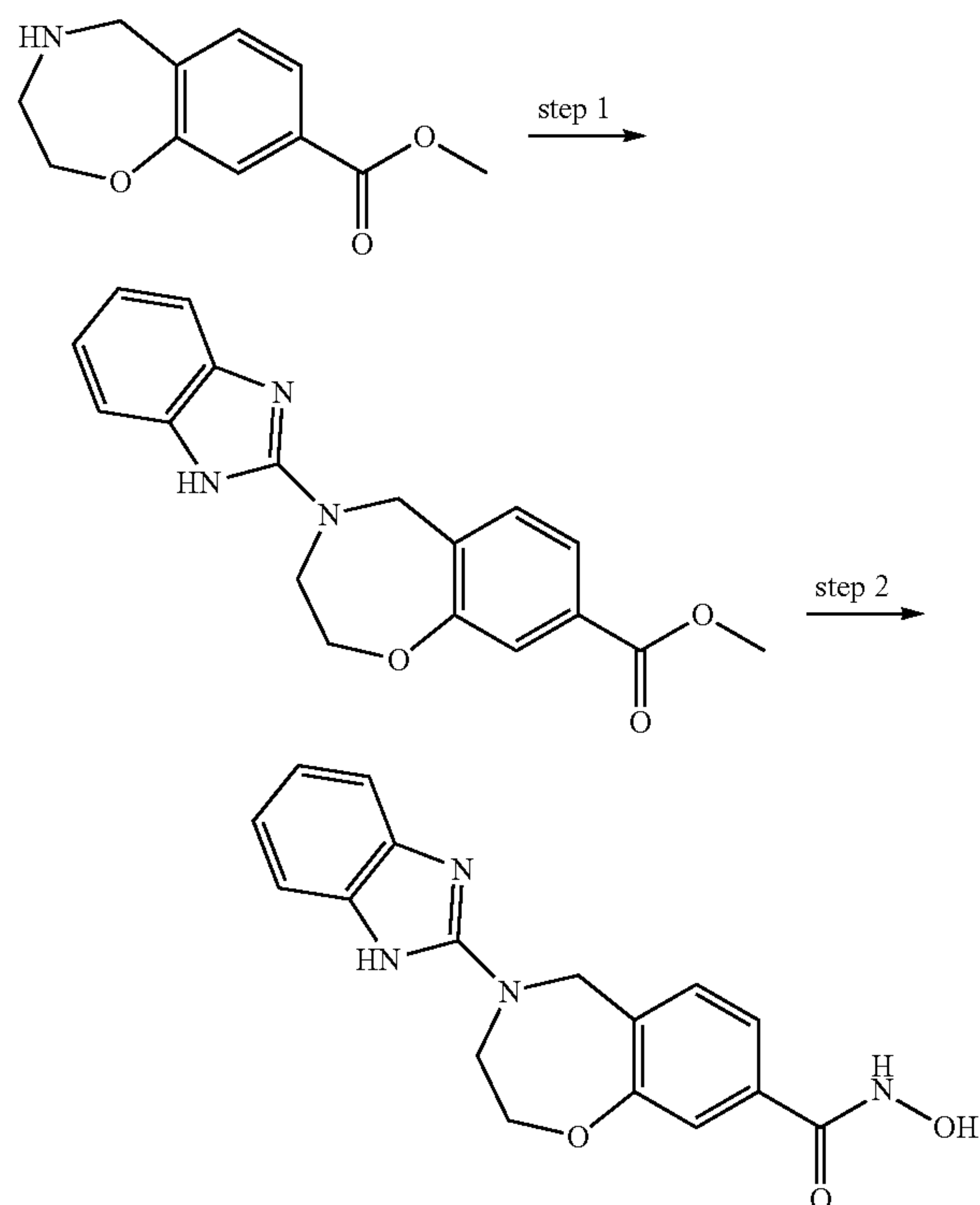


TABLE 38-continued

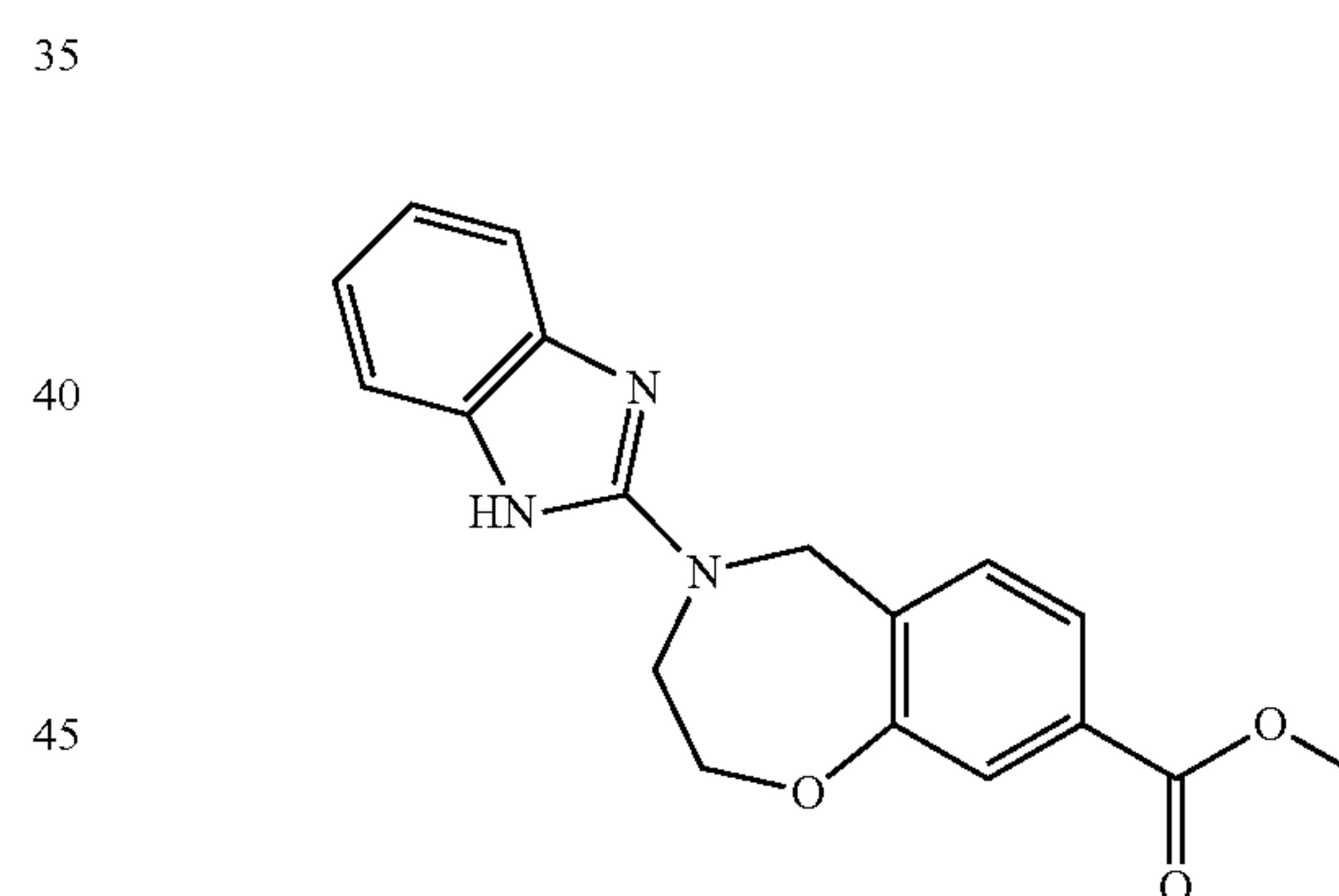
The following compounds were prepared by the parallel synthesis method of Example 82.			
Structure	Found M + H (ES)	Structure	Found M + H (ES)
	265		307
	279		291
	291		

## Example 83

Preparation of 4-(1H-benzo[d]imidazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



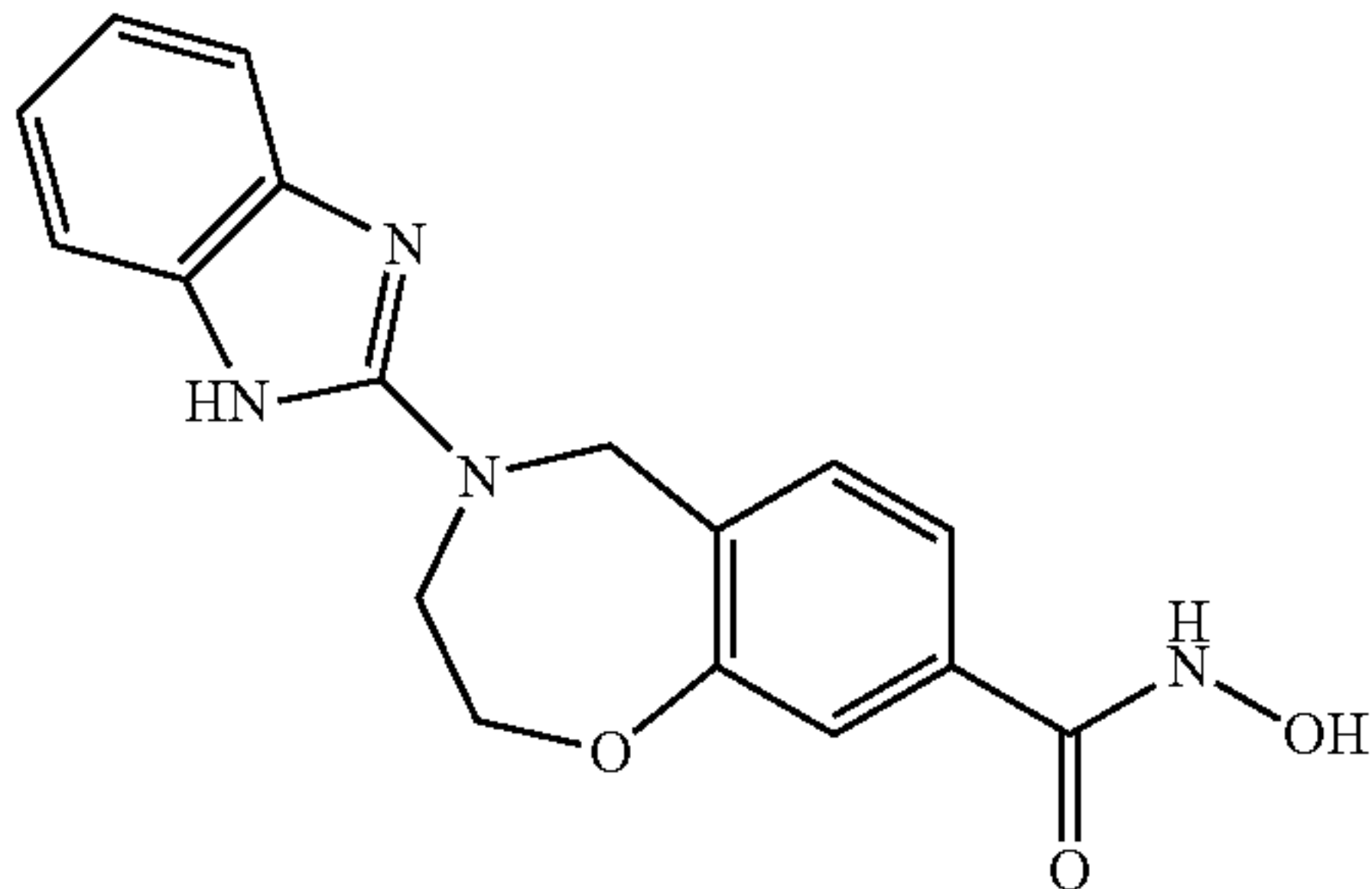
Step-1: Methyl 4-(1H-benzo[d]imidazol-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate



A 2 mL reaction vial was charged with methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (0.2M in 1-butanol, 200  $\mu$ L, 40  $\mu$ mol) and 2-bromo-1H-benzo[d]imidazole (0.2M in 1-butanol, 240  $\mu$ L, 48  $\mu$ mol). Solid  $\text{KH}_2\text{PO}_4$  (21.8 mg, 160  $\mu$ mol) was added and the vial was sealed and shaken at 110° C. overnight. The solvent was removed under reduced pressure and to the residue is added brine (500  $\mu$ L). The mixture was extracted with EtOAc (2 $\times$ 500  $\mu$ L) and the combined organic layers were evaporated to dryness under reduced pressure.

241

Step-2: 4-(1H-benzo[d]imidazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Mixed solvent of THF/MeOH (3:1, 180  $\mu$ L) was added to the vial containing methyl 4-(1H-benzo[d]imidazol-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate and it was shaken at 50° C. for 15 min to dissolve the residue. NH<sub>2</sub>OH (50% in water, 125  $\mu$ L) was added followed by aq. 1N NaOH (85  $\mu$ L) and the vial was sealed and shaken at room temperature overnight. The solvent was evaporated under reduce pressure and the residue was dissolved in DMSO (500  $\mu$ L) then purified by HPLC to afford the title compound (7.0 mg, 54% yield). MS: (ES, m/z): 325 [M+H]<sup>+</sup>.

TABLE 39

The following compounds were prepared by the parallel synthesis method of Example 83.	
Structure	Found M + H (ES)
	325
	383

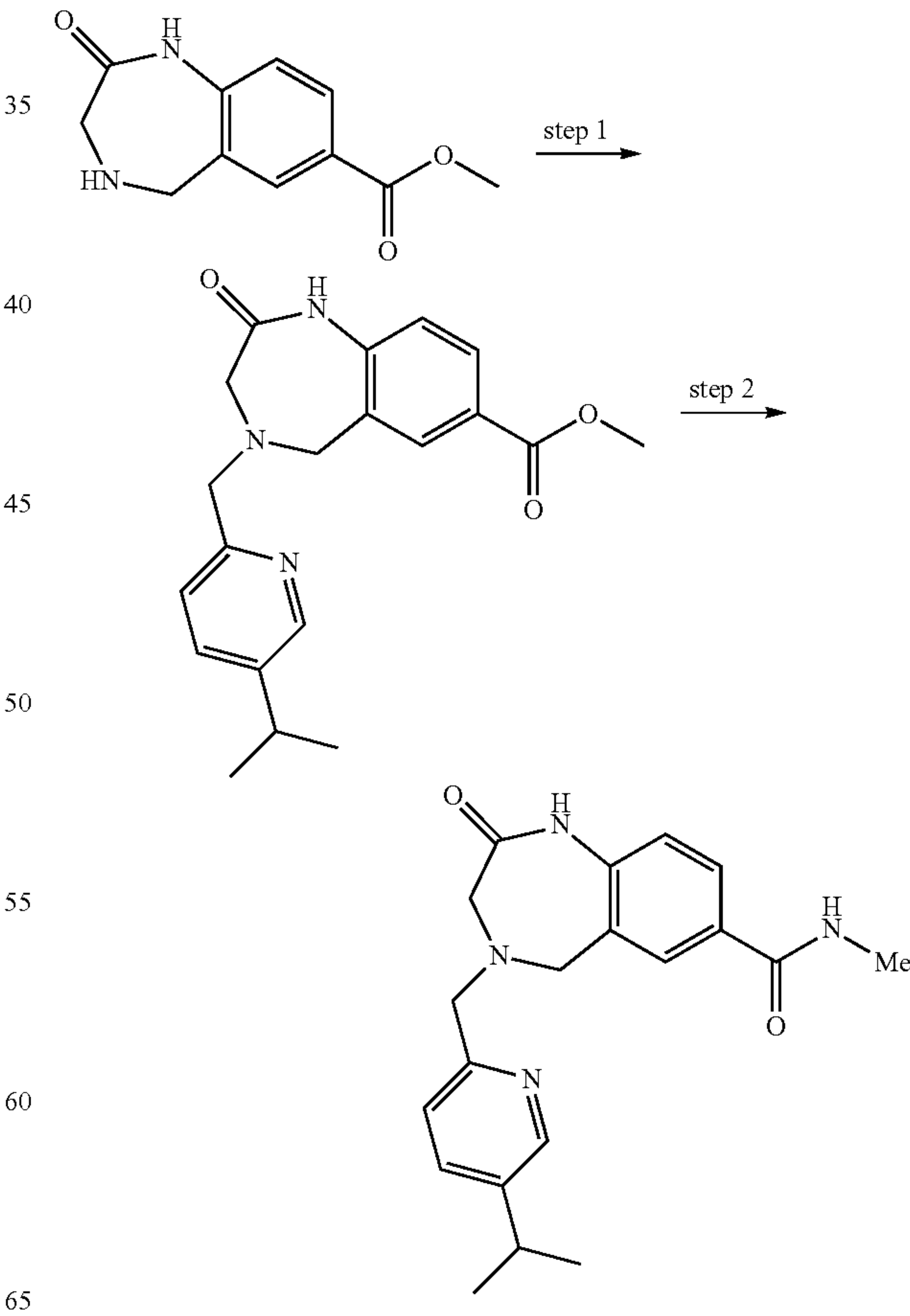
242

TABLE 39-continued

The following compounds were prepared by the parallel synthesis method of Example 83.	
Structure	Found M + H (ES)
	383

Example 84

Preparation of N-hydroxy-4-((5-isopropylpyridin-2-yl)methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide





## 243

Step-1: Methyl 4-(4-isopropylbenzyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate

A 2 mL reaction vial was charged with methyl 2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate (0.2 M in N,N-dimethylacetamide, 150  $\mu$ L, 30  $\mu$ mol) and 5-isopropylpicolinaldehyde (0.2 M in 1,2-dichloroethane, 225  $\mu$ L, 45  $\mu$ mol). The vial was sealed and shaken at room temperature for 1 h. Sodium triacetoxyborohydride (0.2M in 1,2-dichloroethane, 500  $\mu$ L, 100  $\mu$ mol) was added and the vial was shaken at room temperature overnight. Half volume of the solvent was removed under reduced pressure. The reaction mixture was diluted with 1N NaOH in brine (500  $\mu$ L) and extracted with EtOAc (2x500  $\mu$ L). The combined organic layers were evaporated to dryness under reduced pressure.

## 244

Step-2: N-hydroxy-4-((5-isopropylpyridin-2-yl)methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide

Mixed solvent of THF/MeOH (3:1, 180  $\mu$ L) was added to the vial containing methyl 4-(4-isopropylbenzyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxylate and it was shaken at 50° C. for 15 min to dissolve the residue. NH<sub>2</sub>OH (50% in water, 125  $\mu$ L) was added followed by aq. 1N NaOH (85  $\mu$ L) and the vial was sealed and shaken at room temperature overnight. The solvent was evaporated under reduce pressure and the residue was dissolved in DMSO (500  $\mu$ L) then purified by HPLC to afford the title compound (1.6 mg, 15% yield). MS: (ES, m/z): 355 [M+H]<sup>+</sup>.

TABLE 40

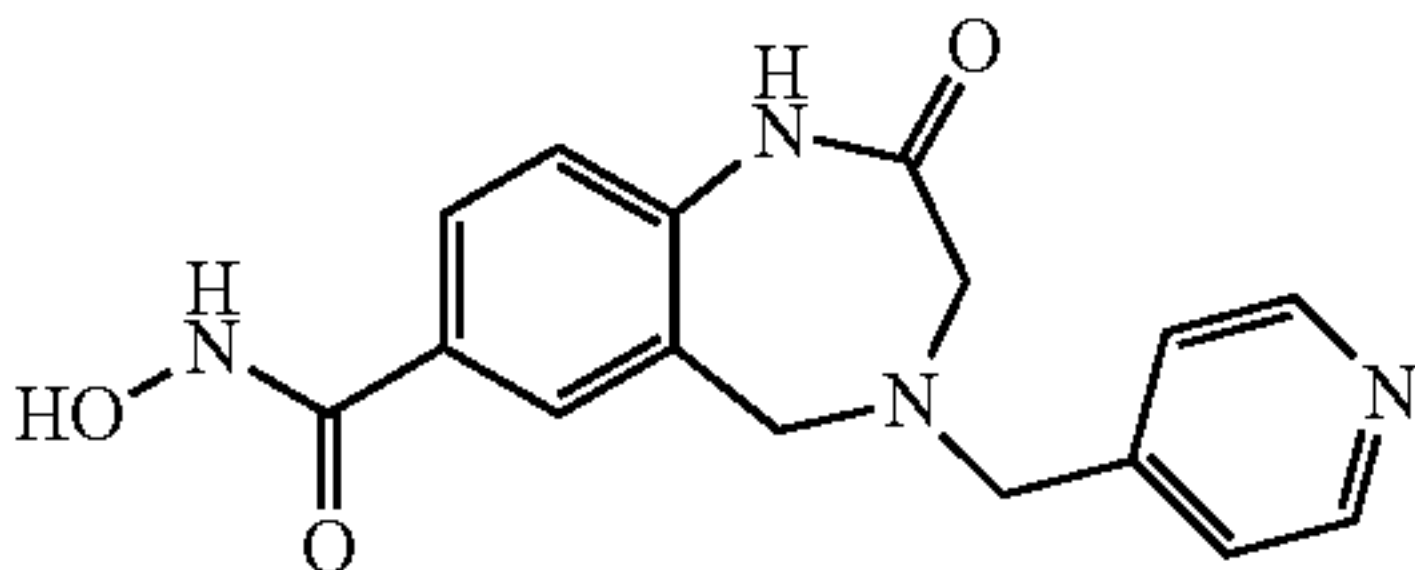
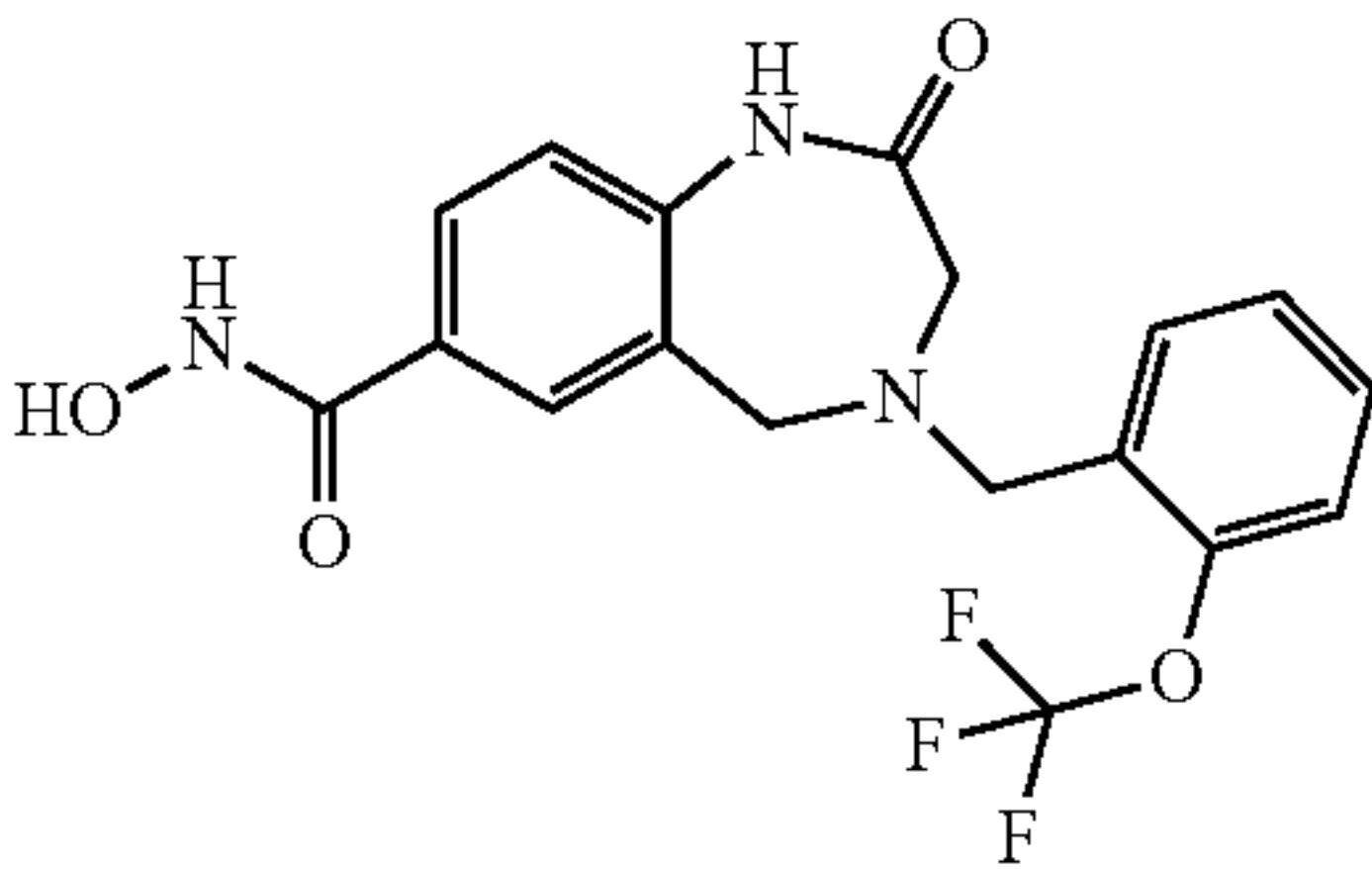
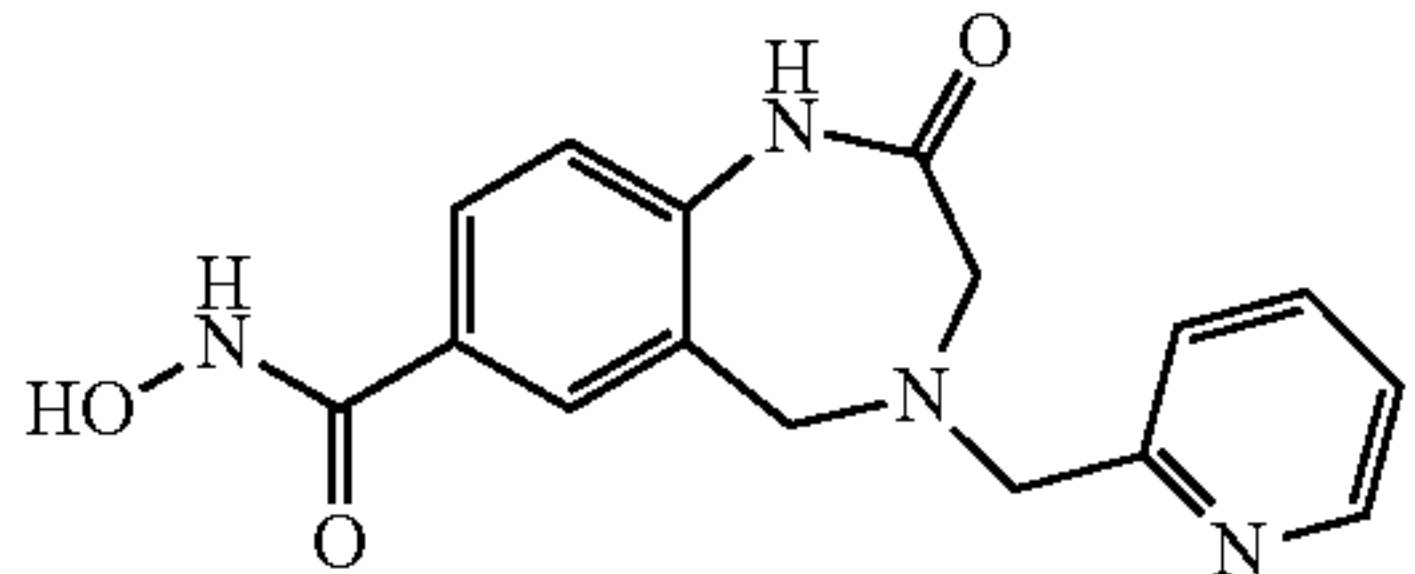
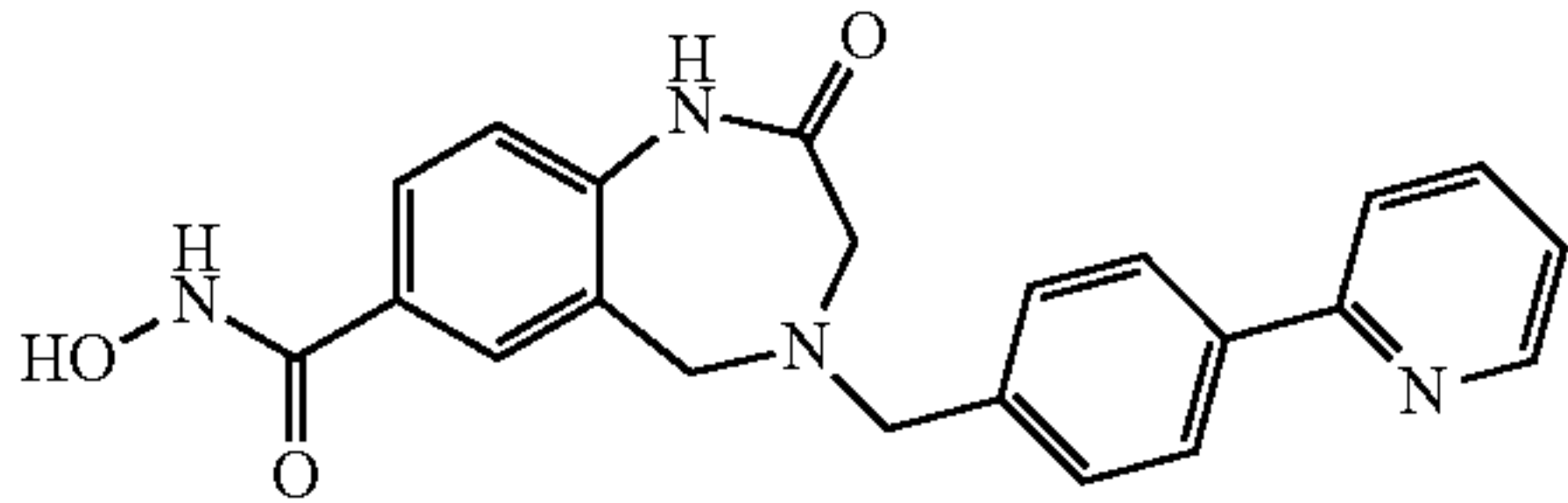
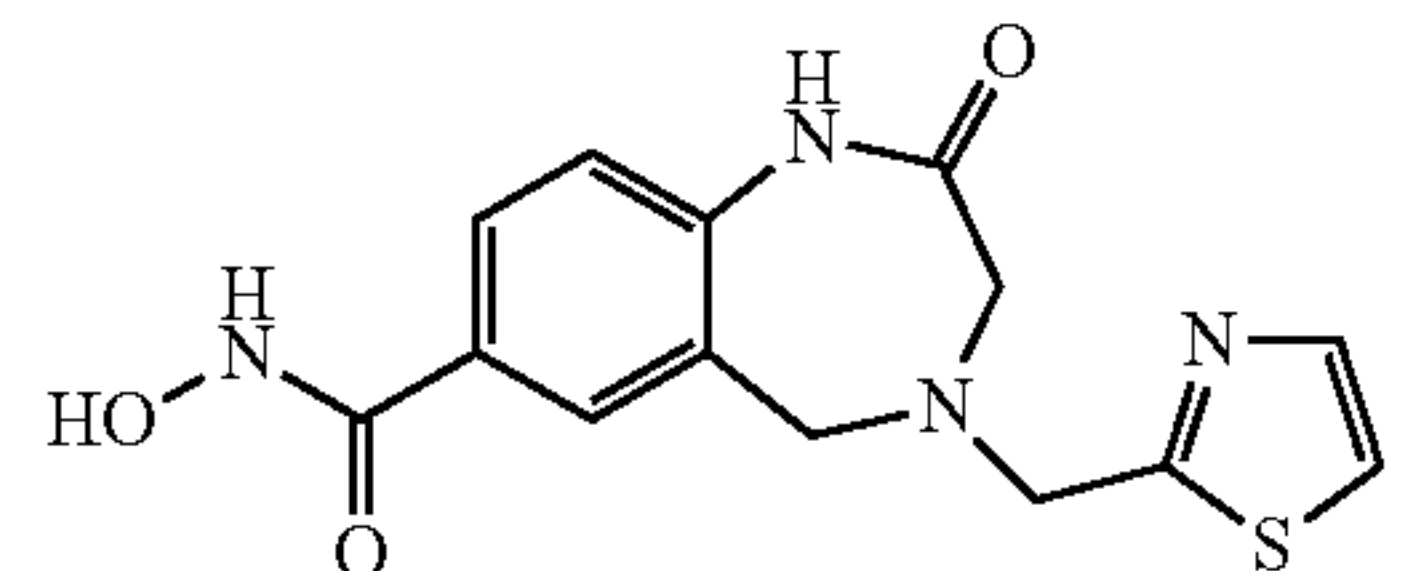
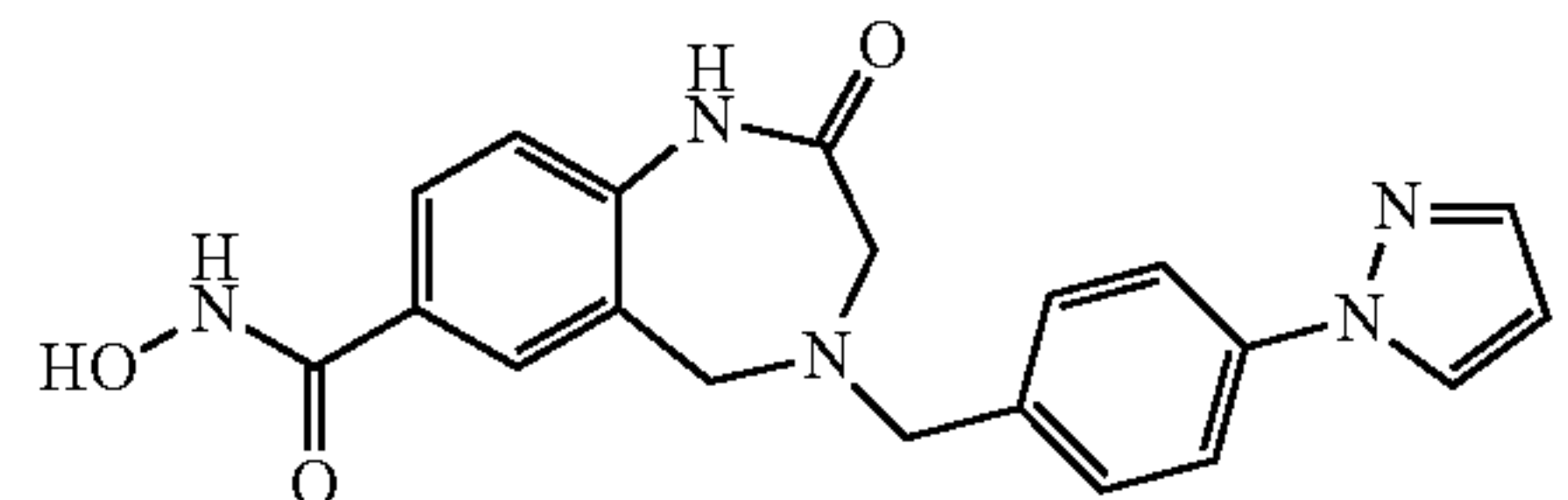
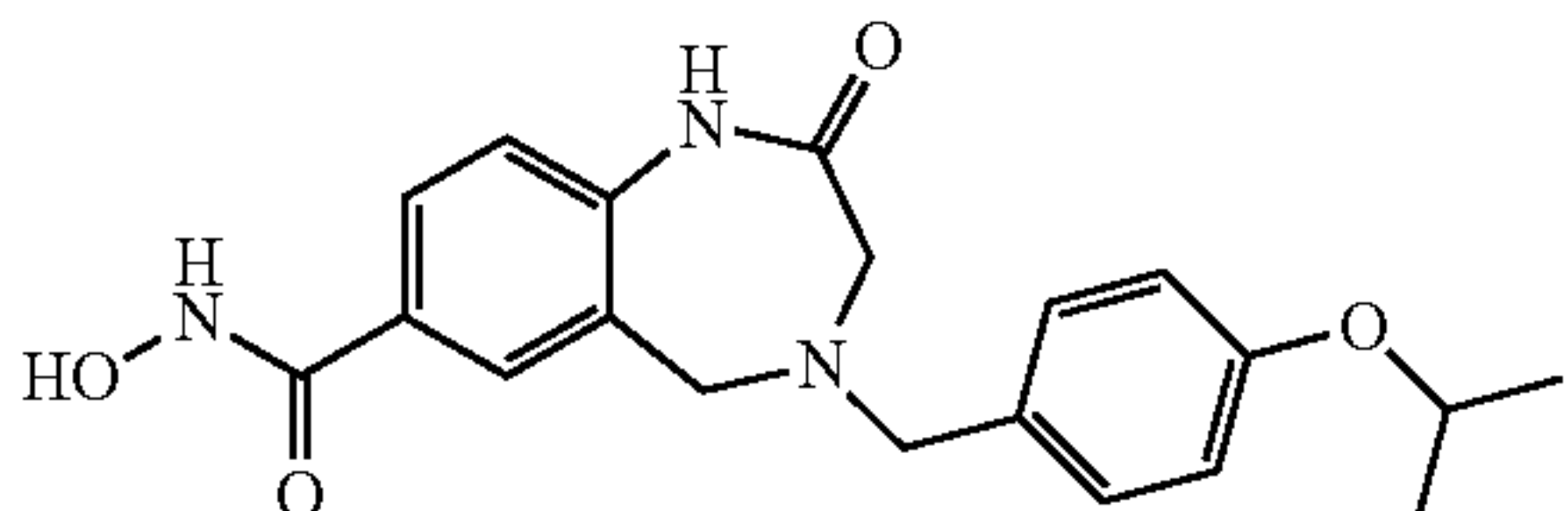
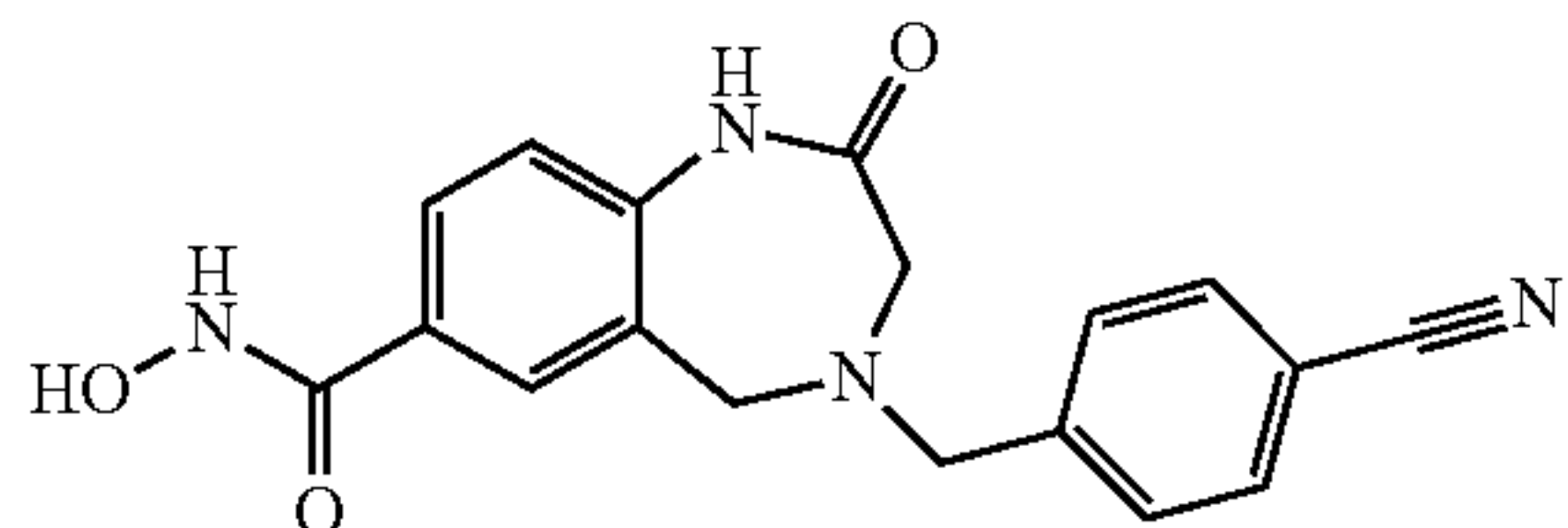
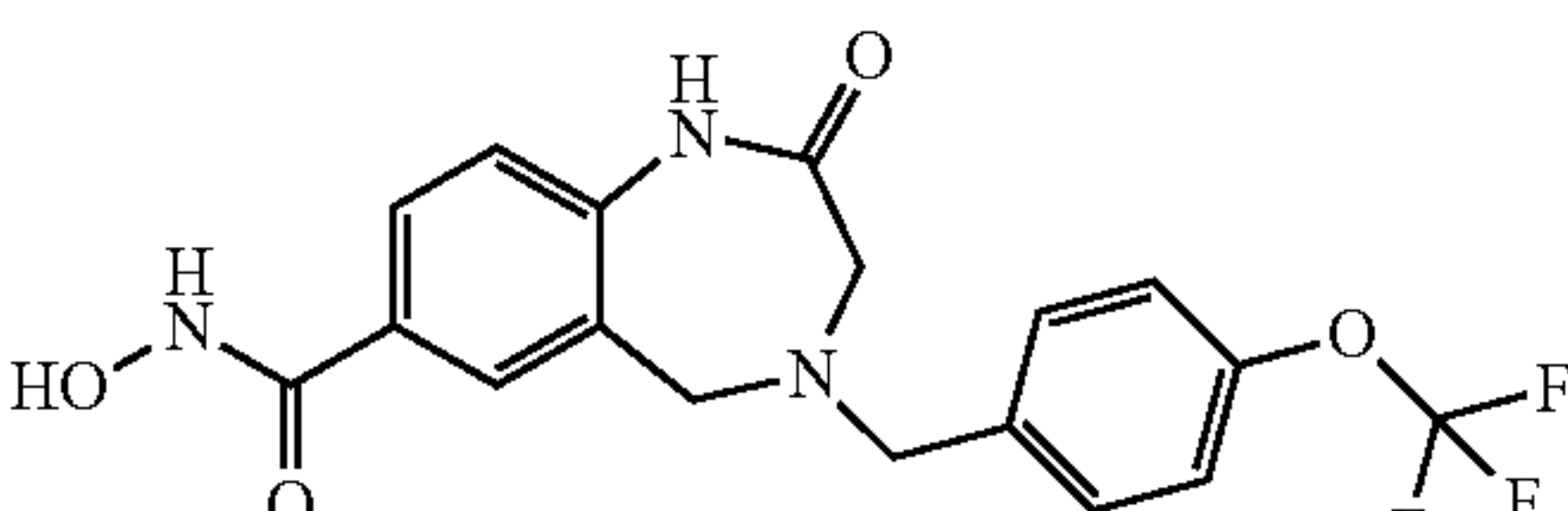
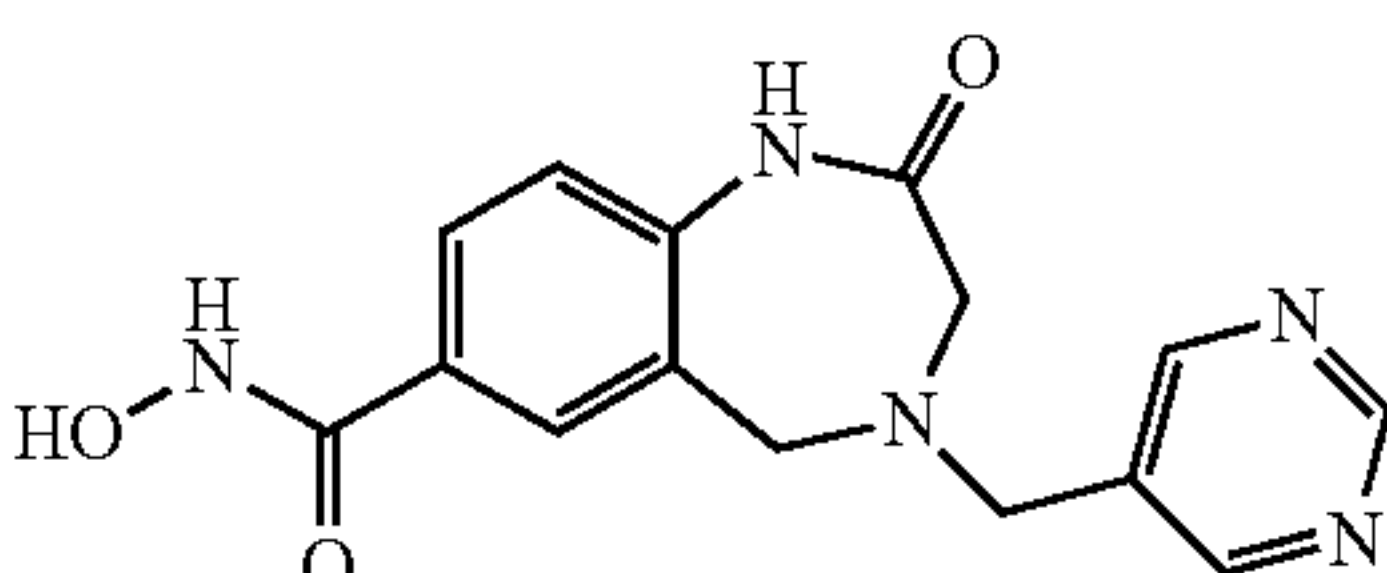
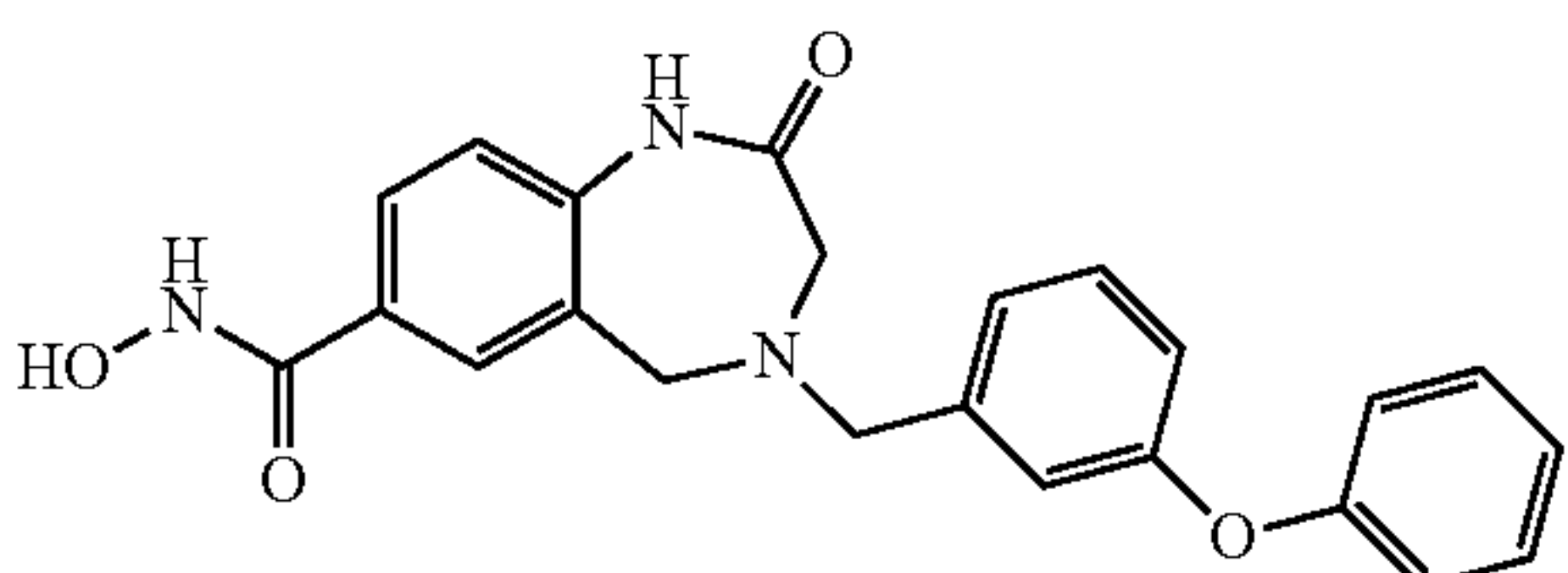
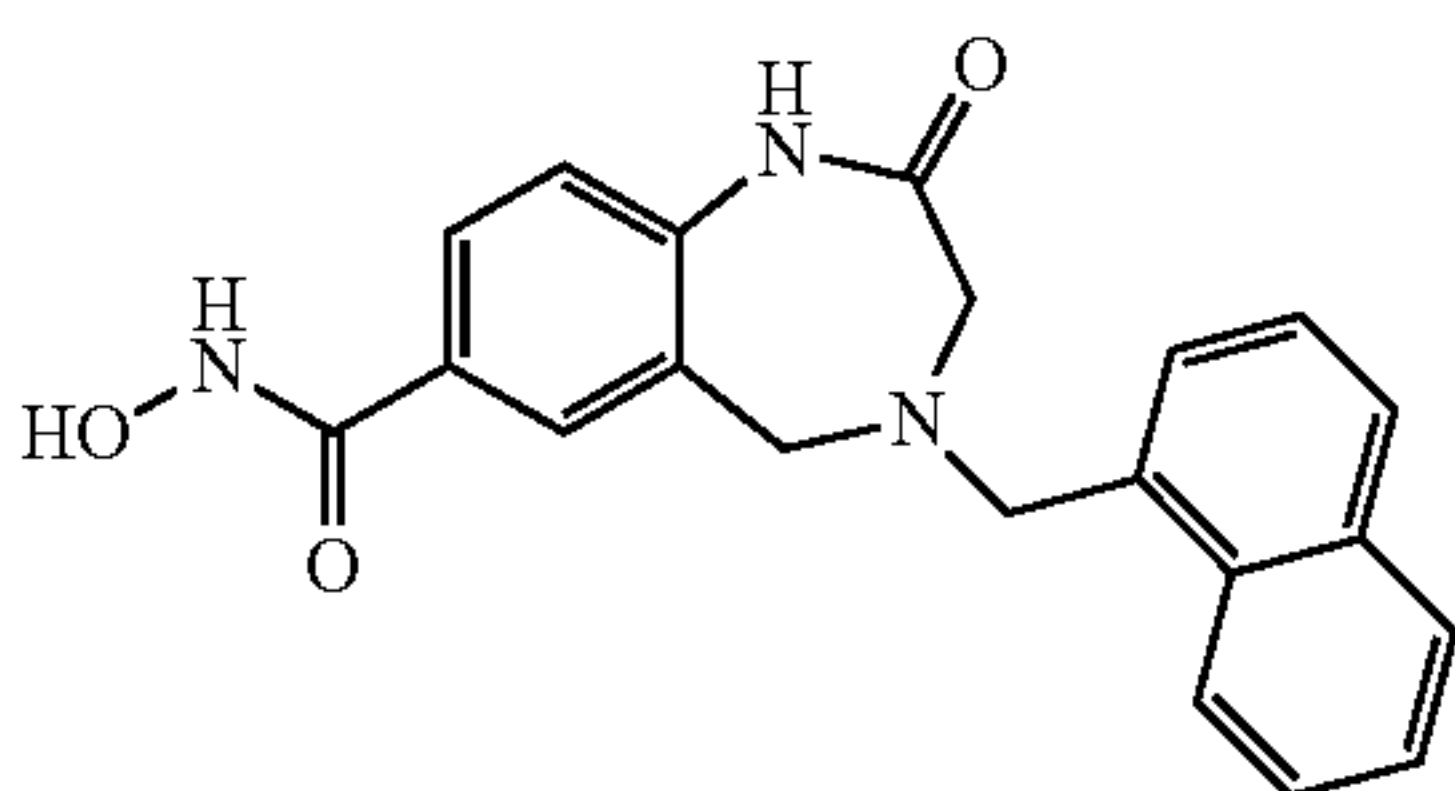
The following compounds were prepared by the parallel synthesis method of Example 84.			
Structure	Found M + H (ES)	Structure	Found M + H (ES)
	313		396
	313		389
	319		378
	370		337
	396		314
	404		362

TABLE 40-continued

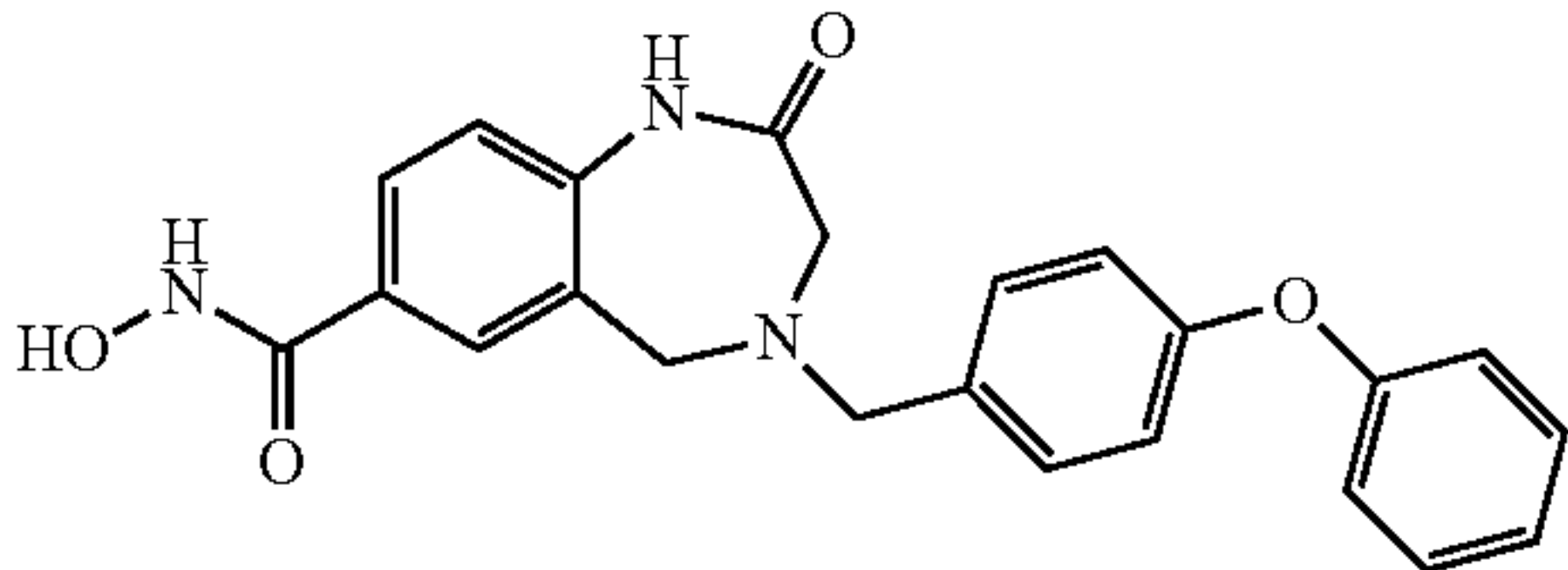
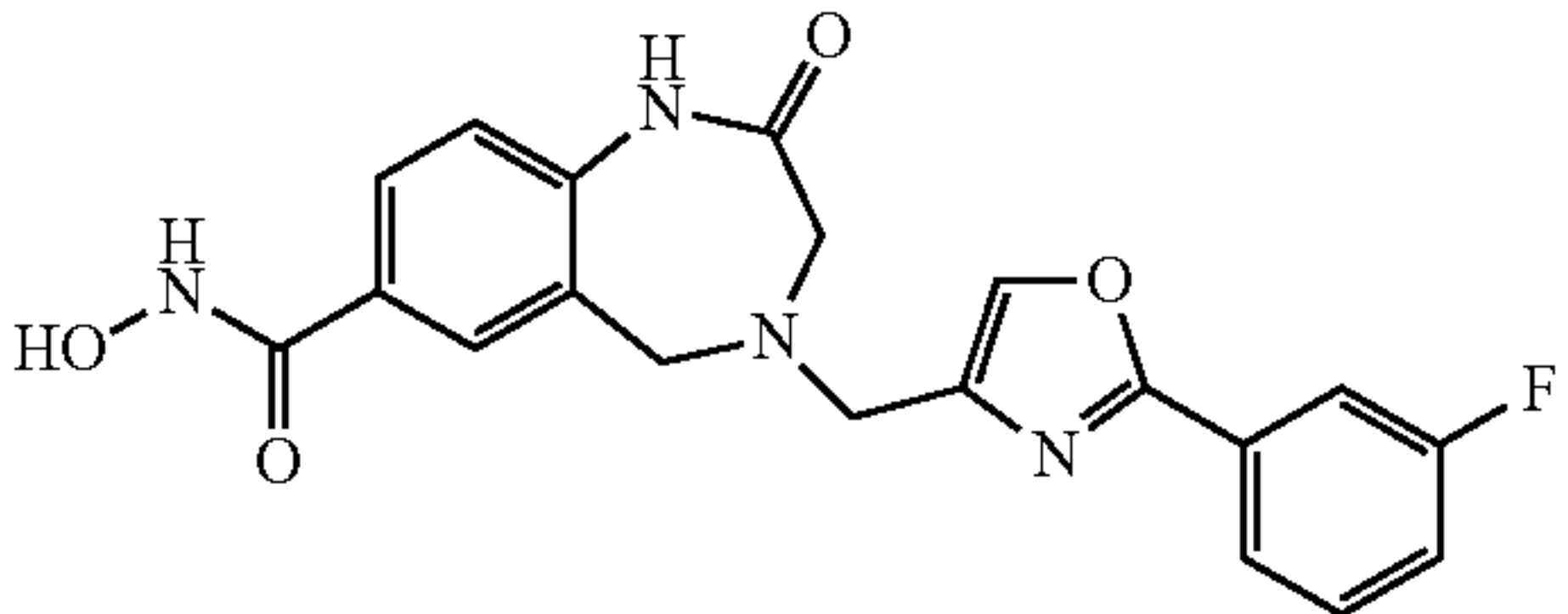
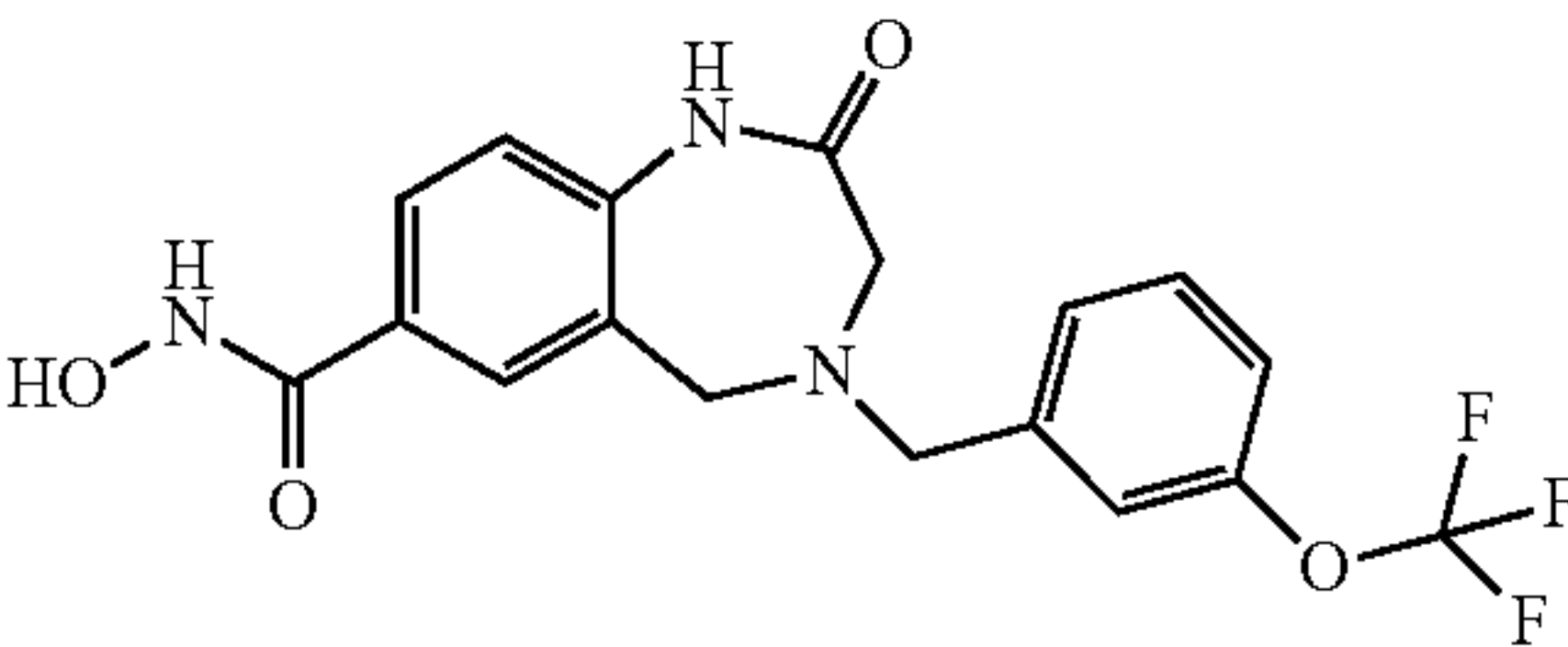
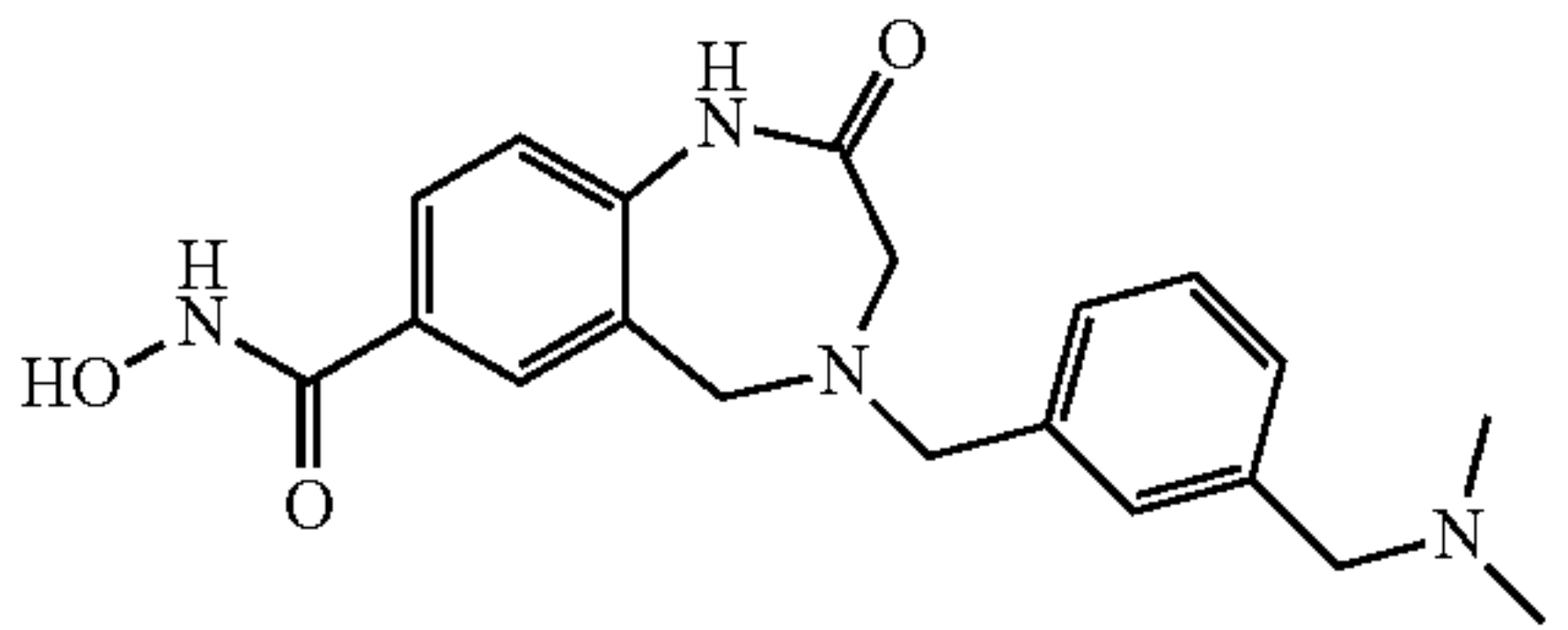
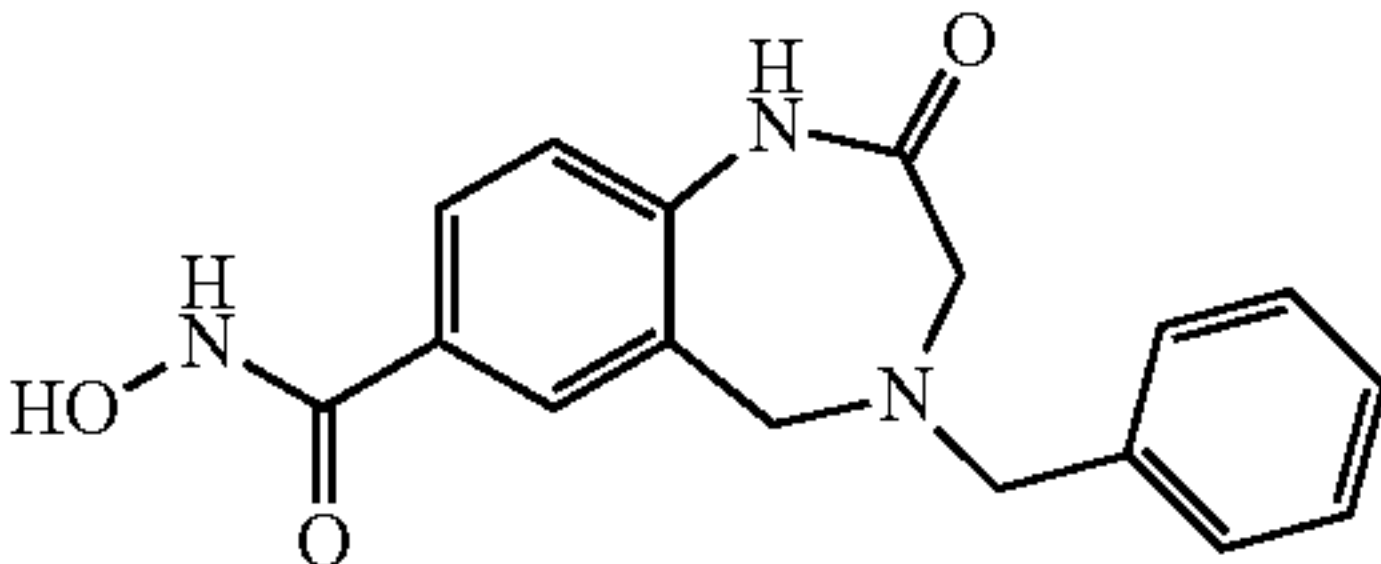
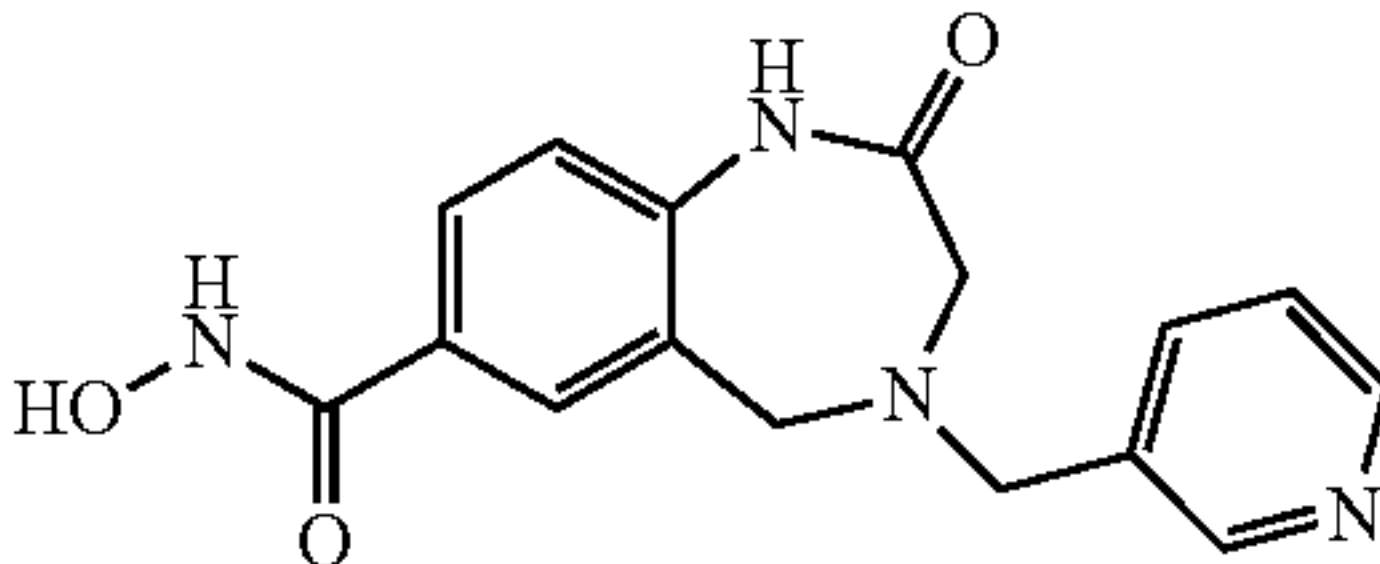
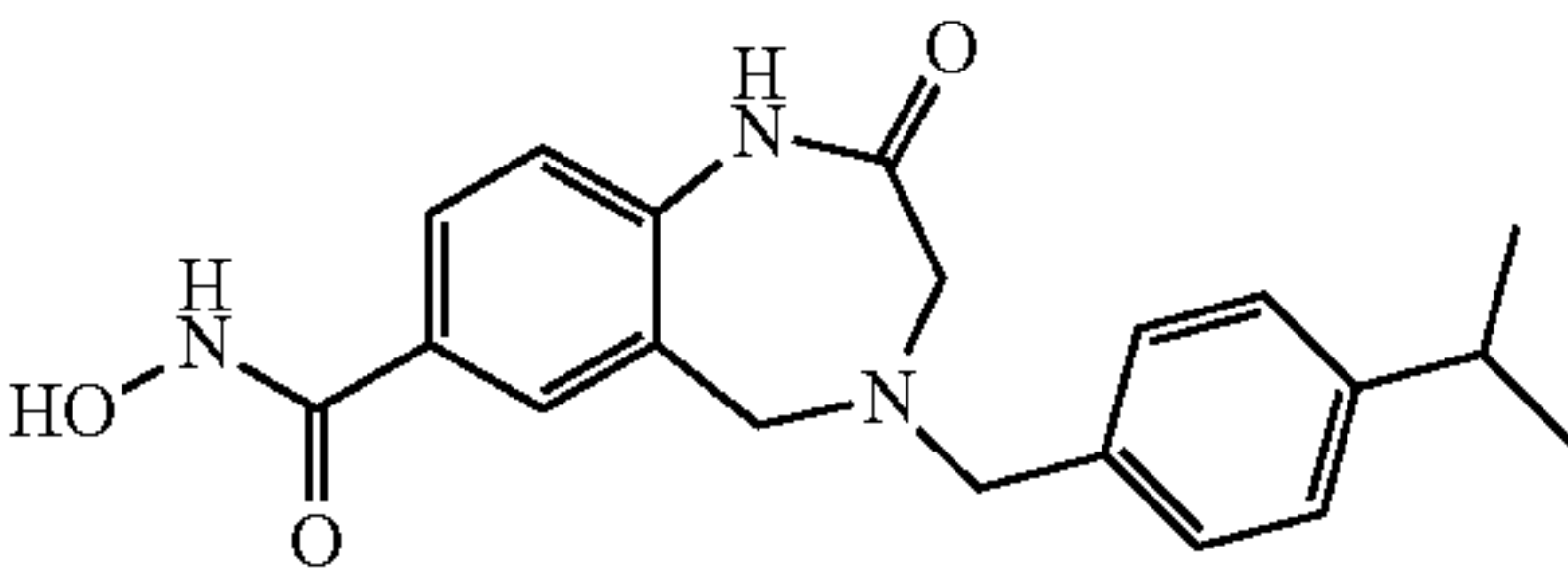
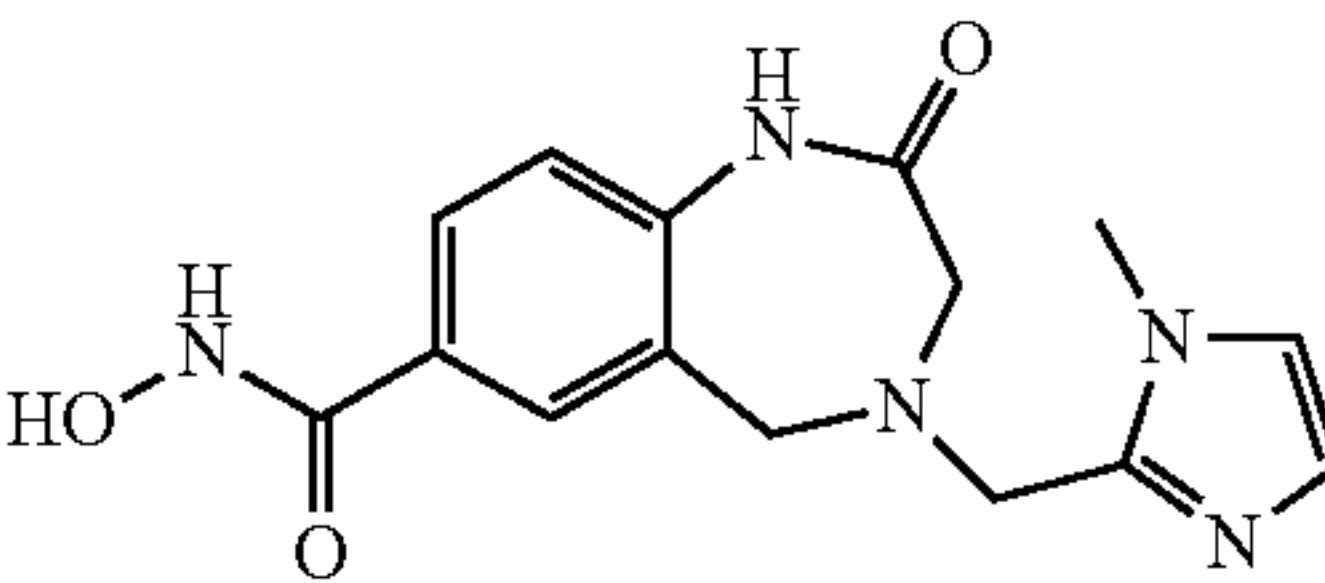
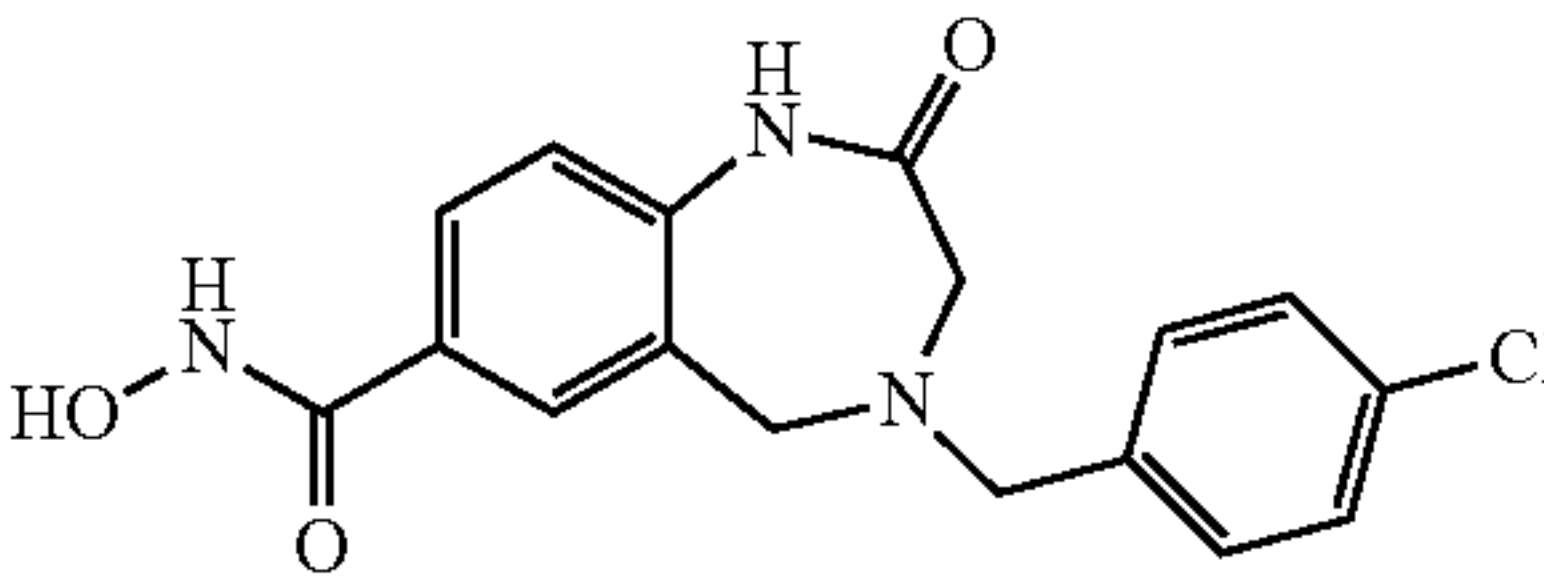
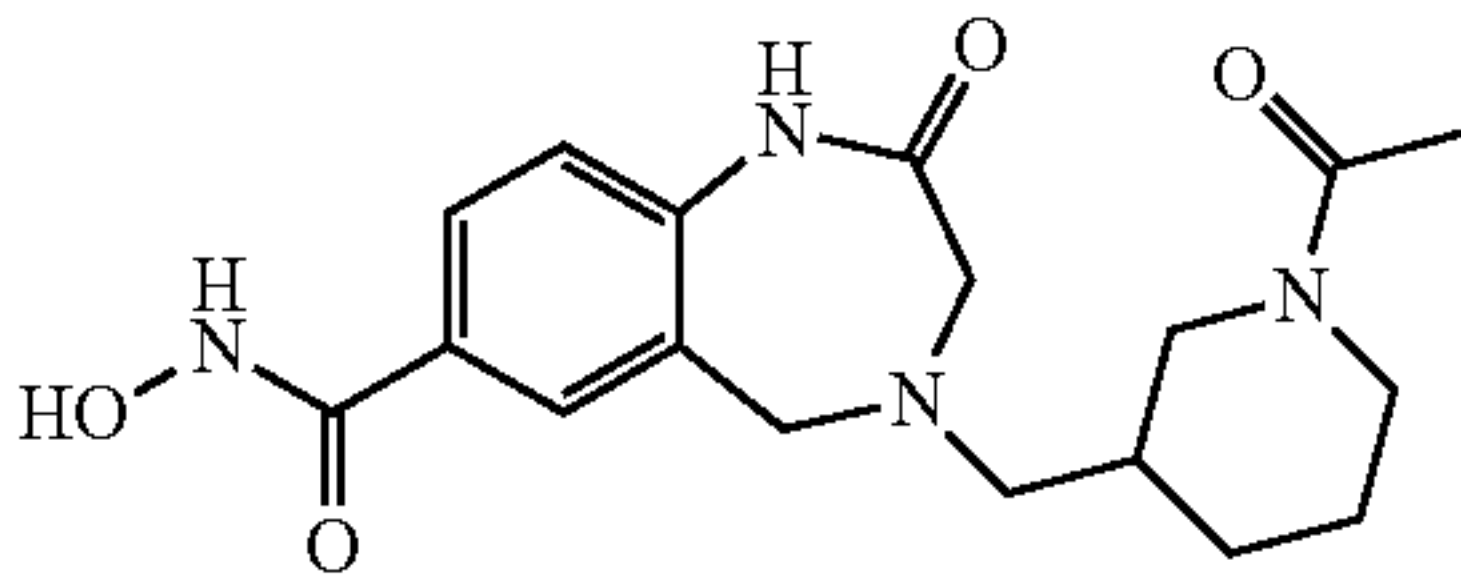
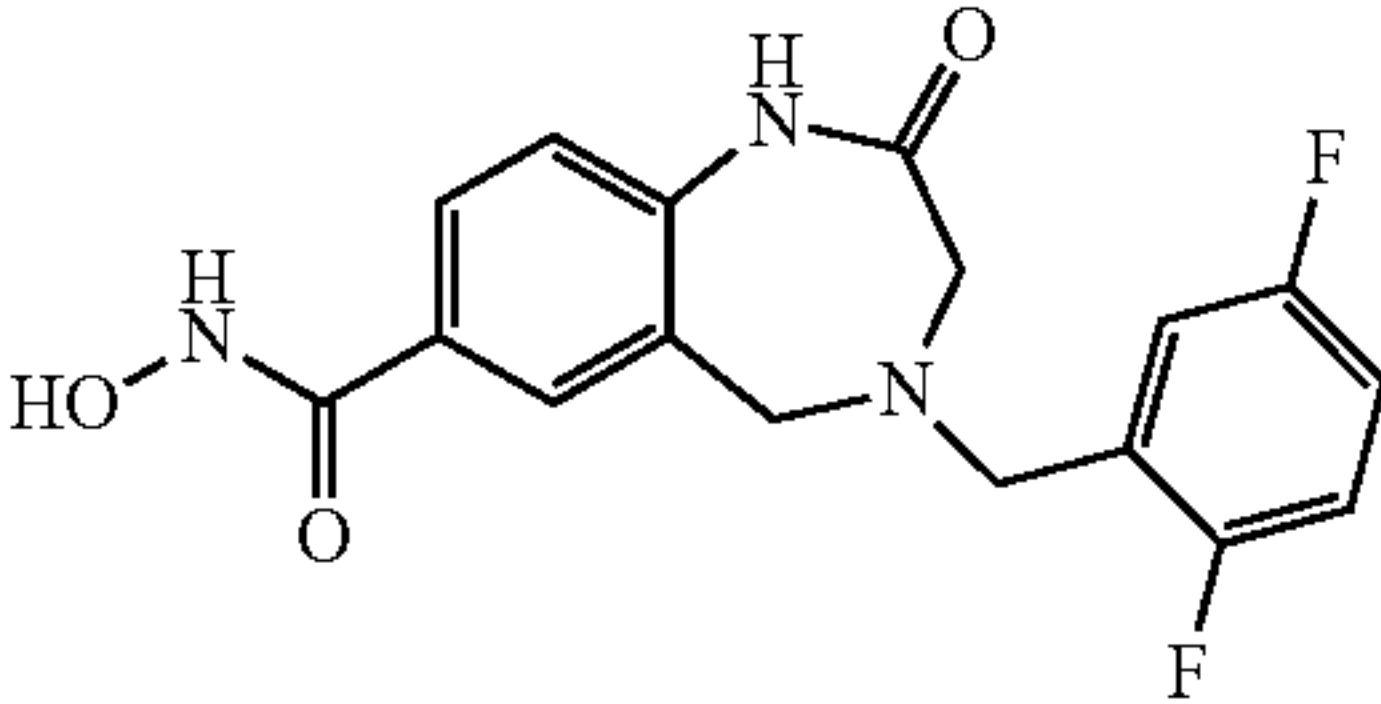
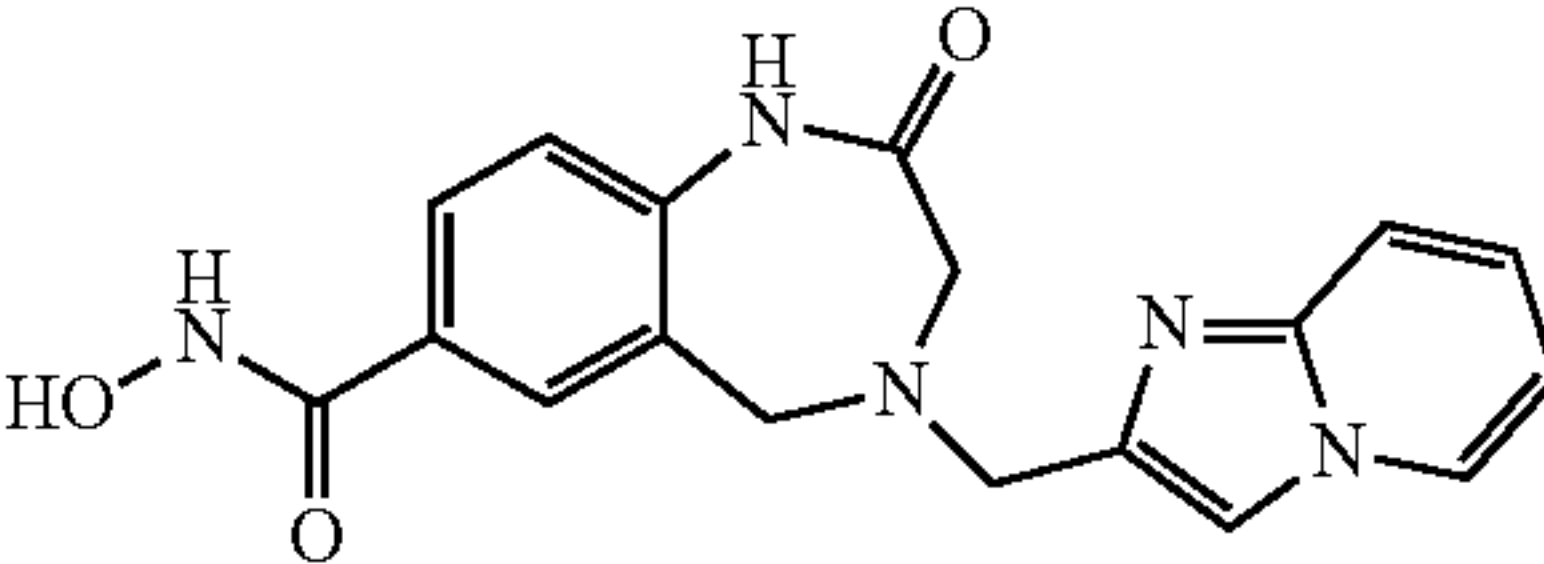
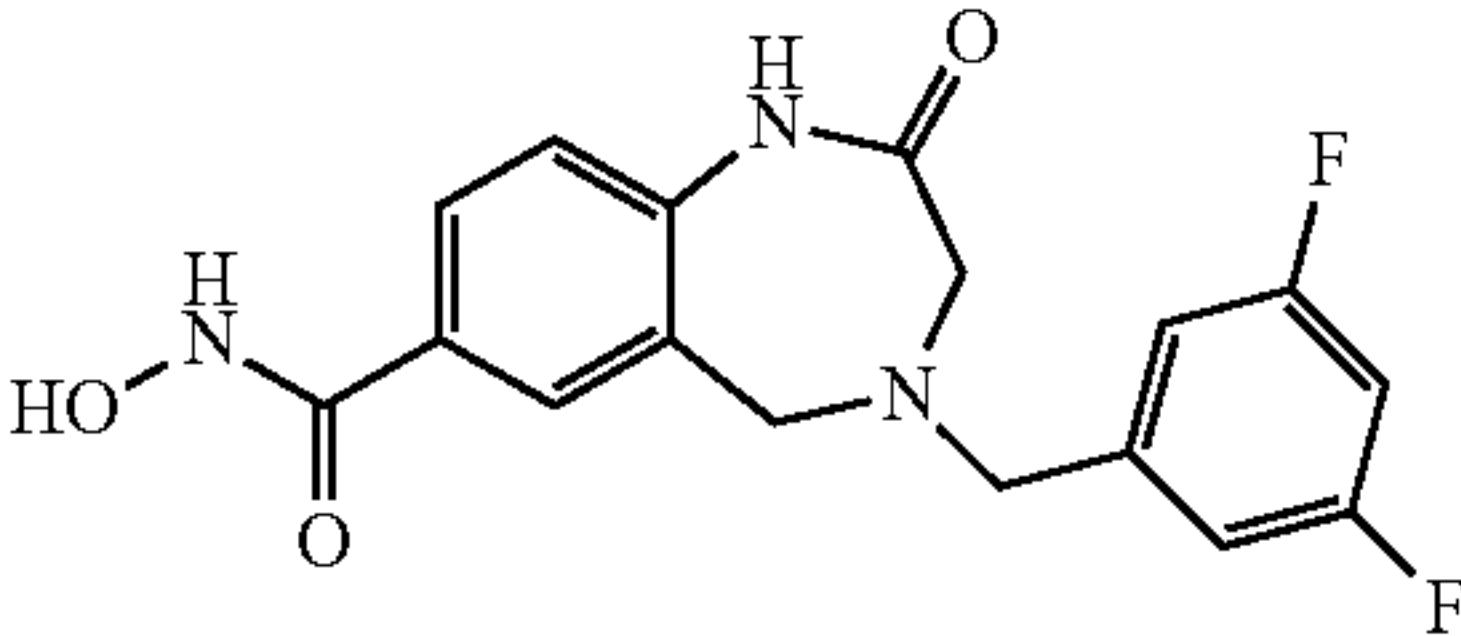
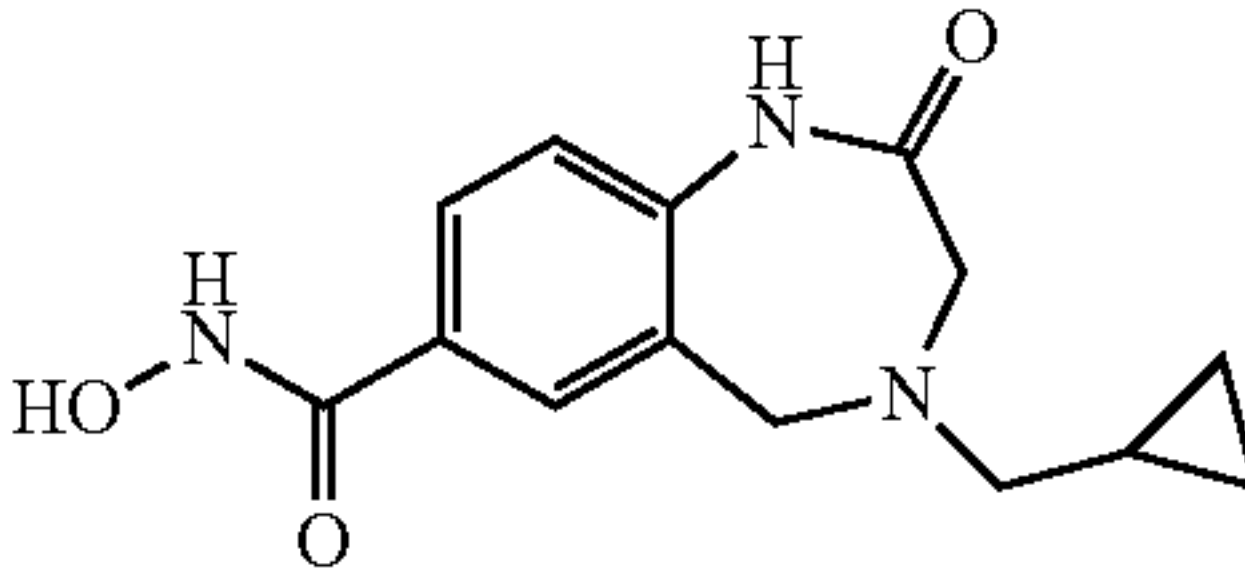
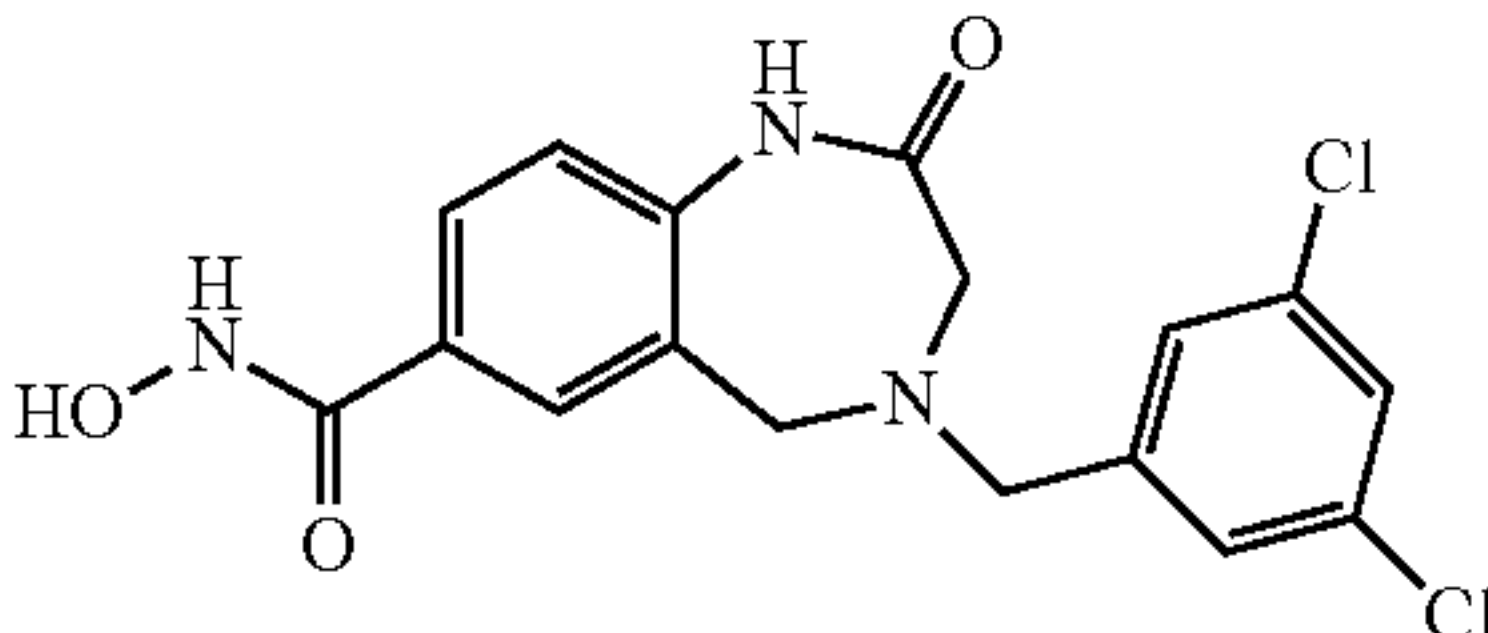
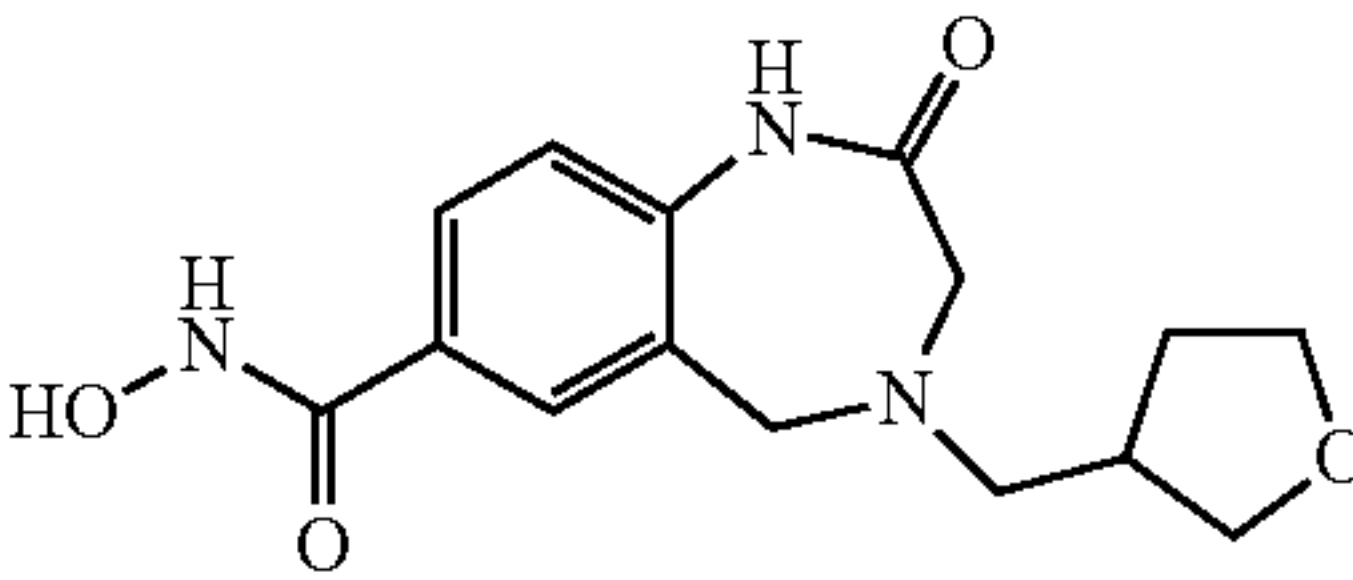
The following compounds were prepared by the parallel synthesis method of Example 84.			
Structure	Found M + H (ES)	Structure	Found M + H (ES)
	404		397
	396		369
	312		313
	354		316
	346		361
	348		352
	348		276
	380		306



TABLE 40-continued

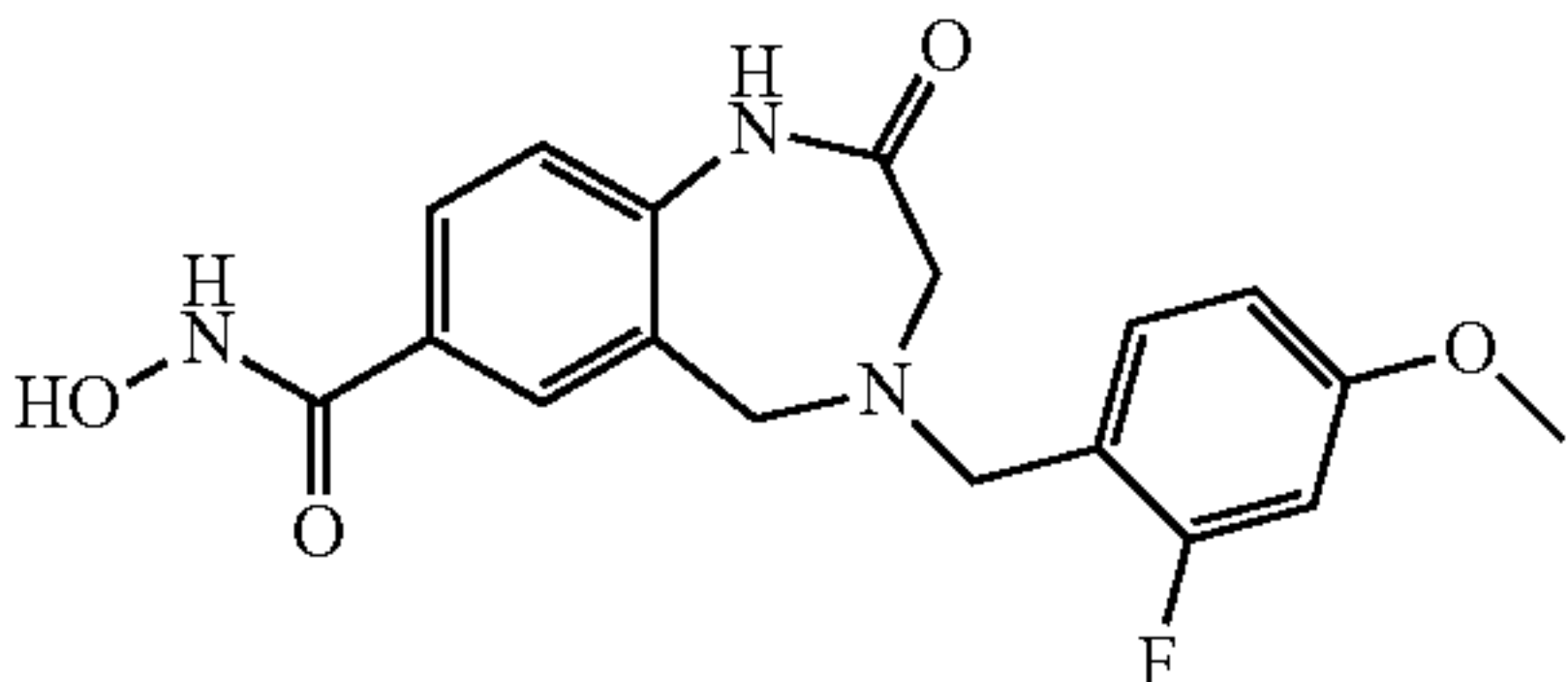
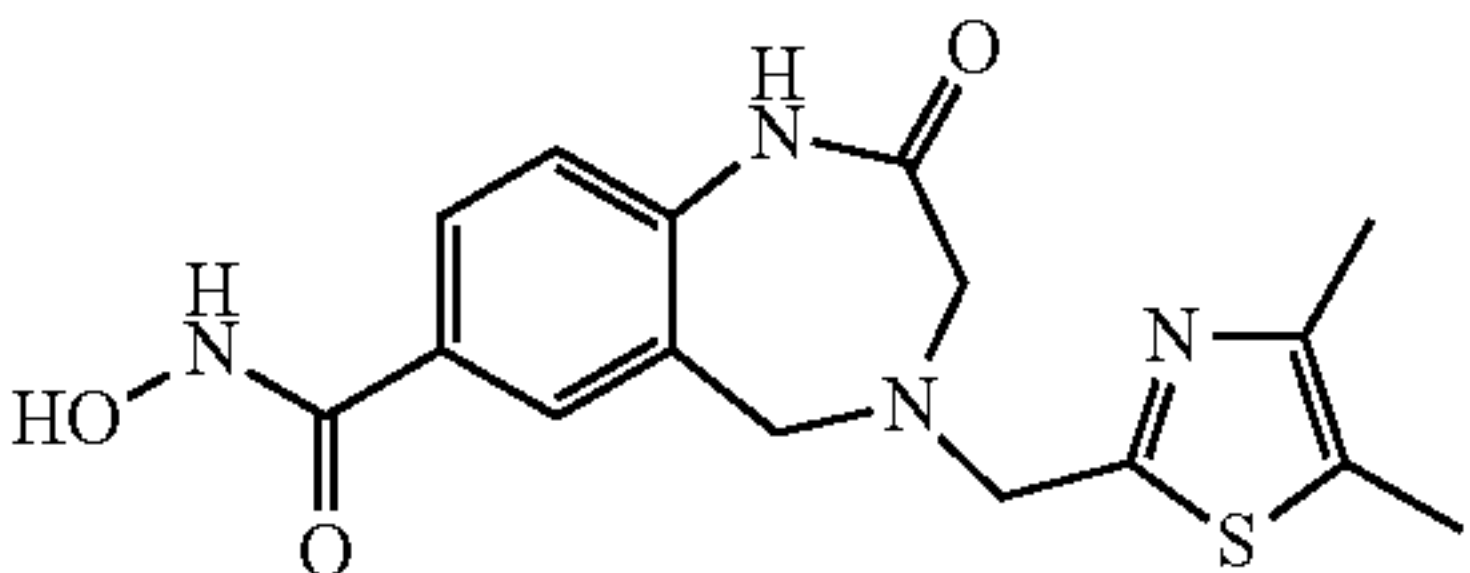
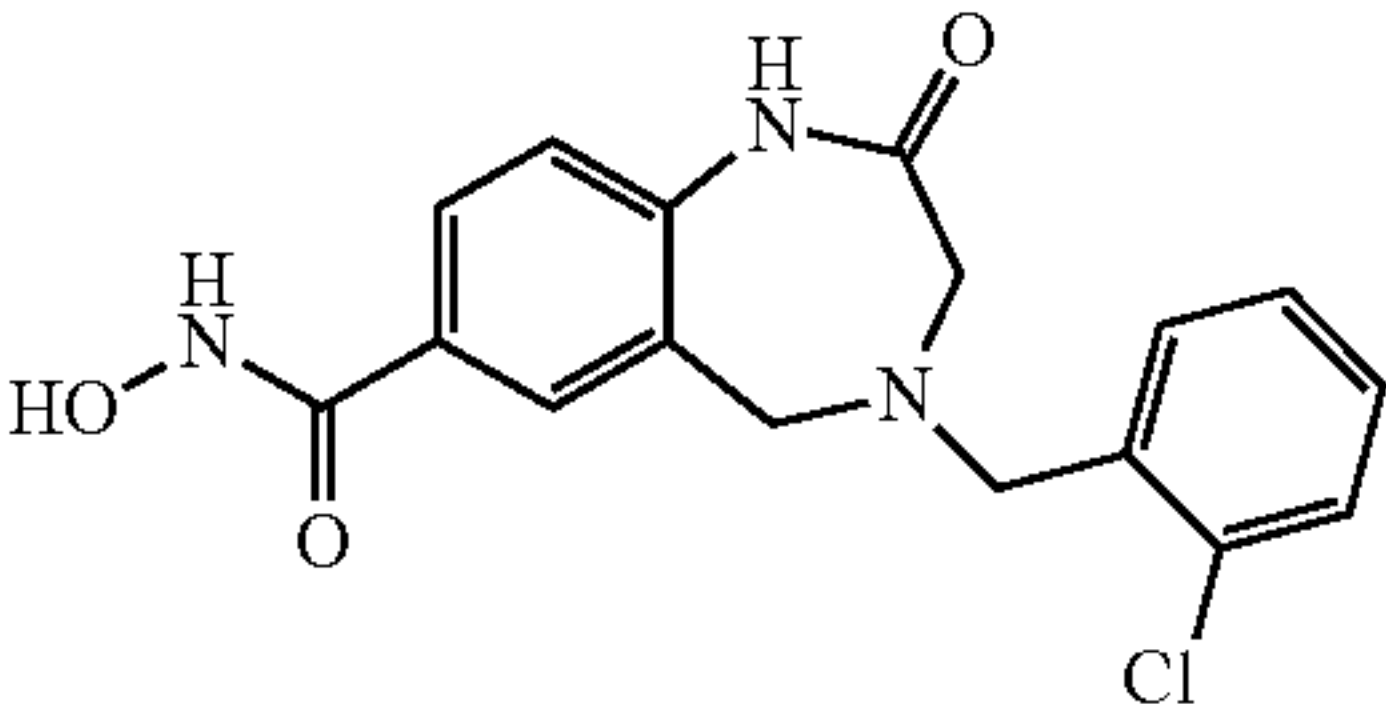
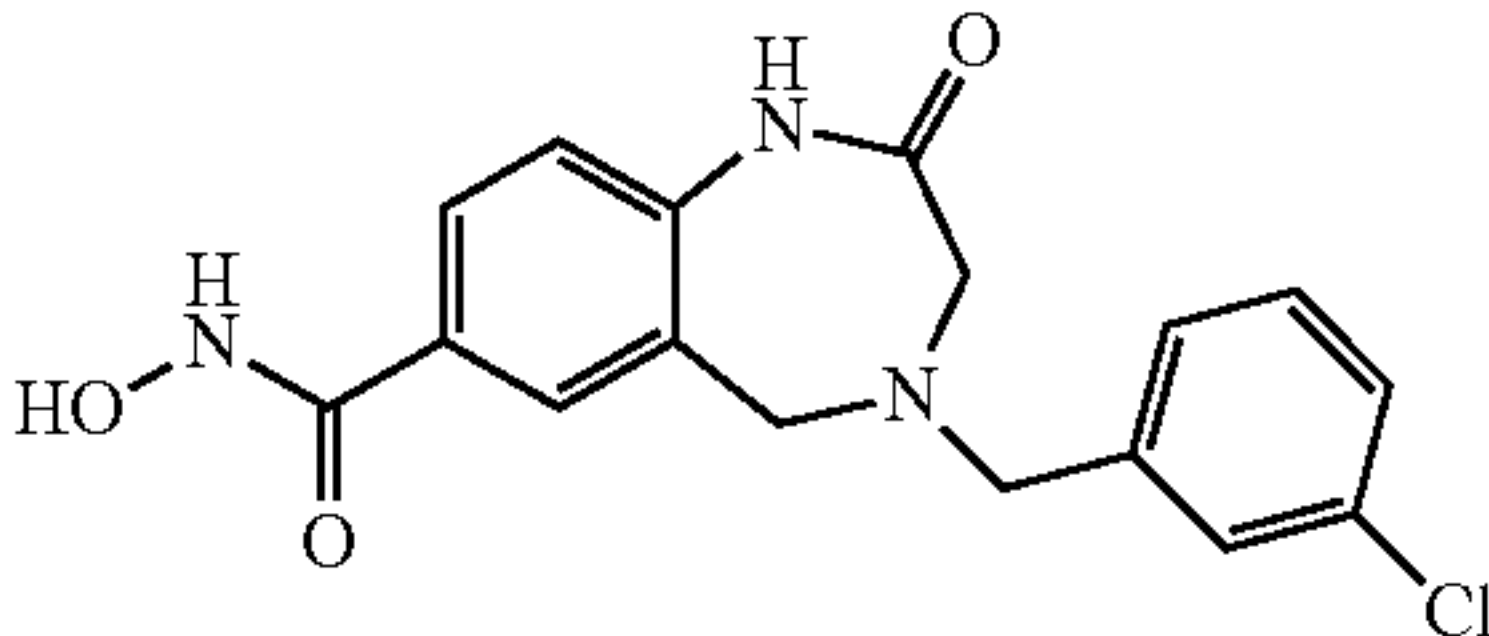
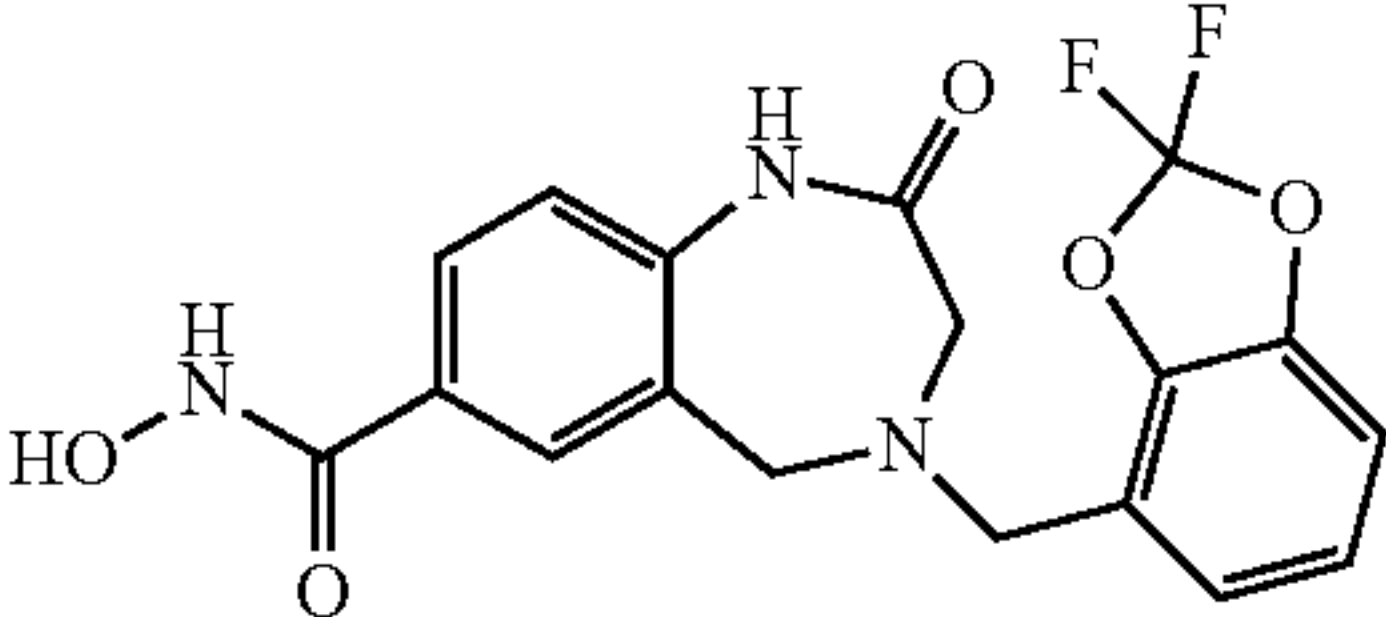
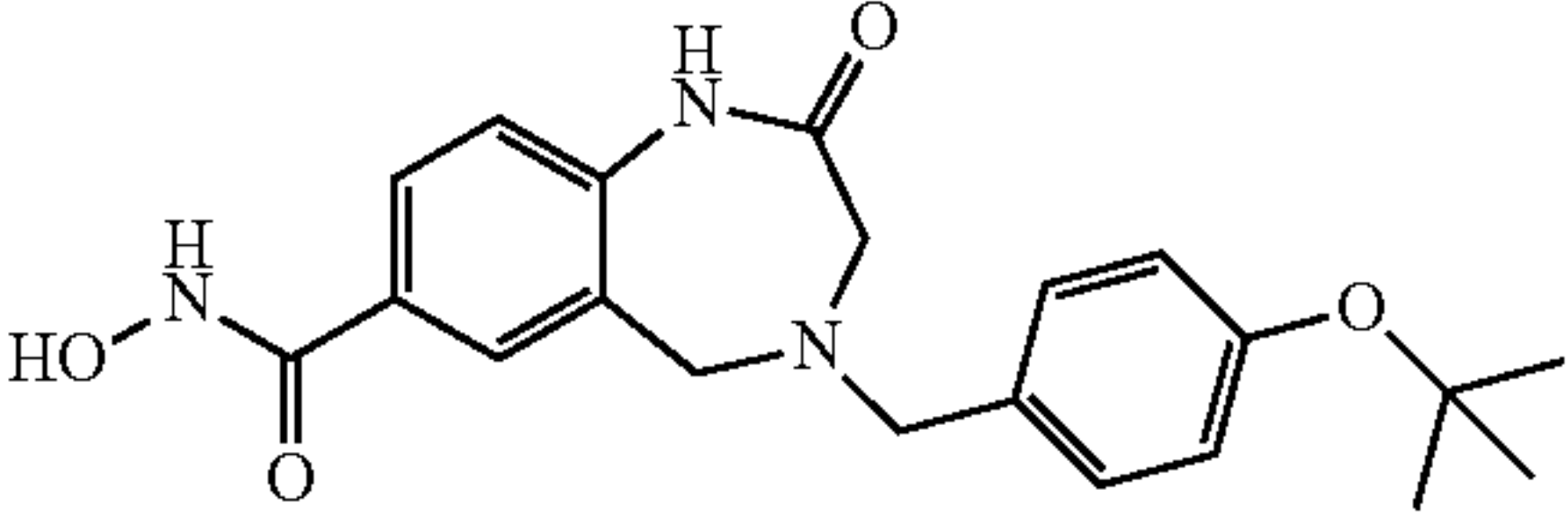
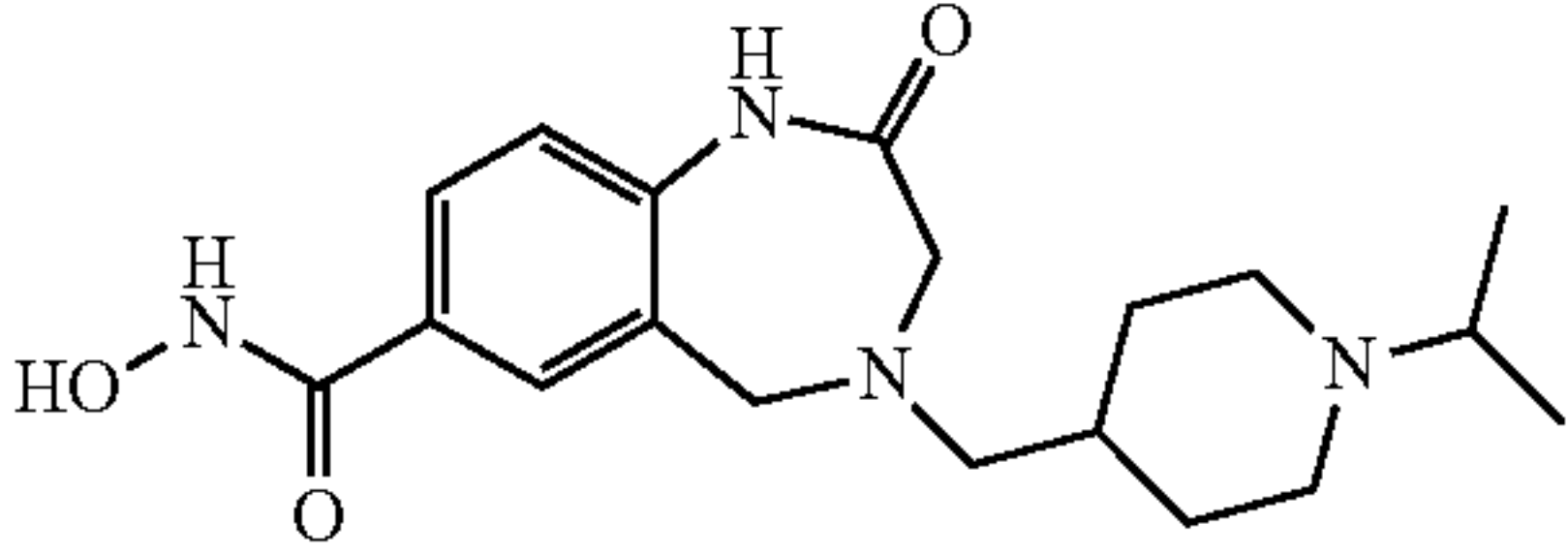
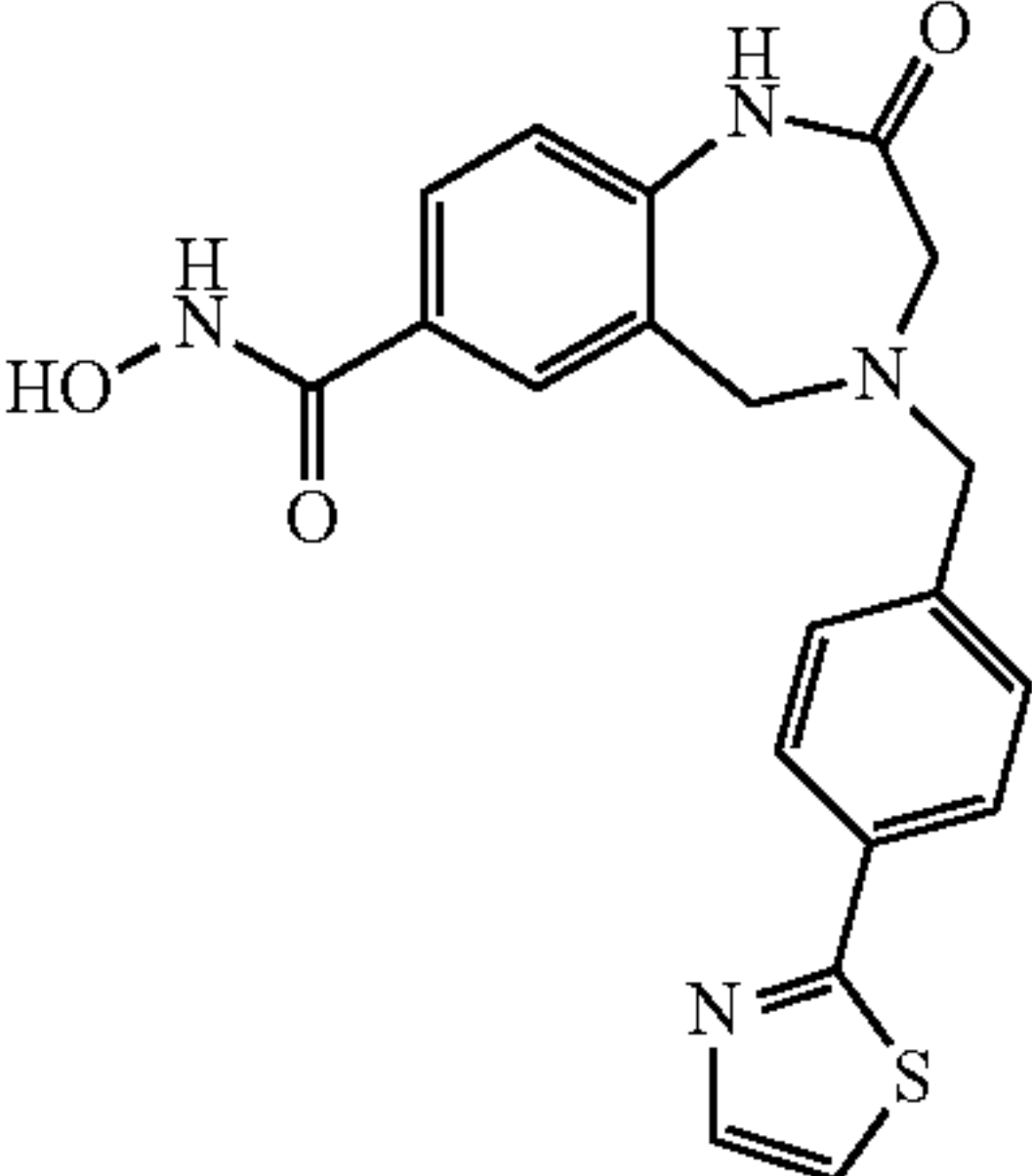
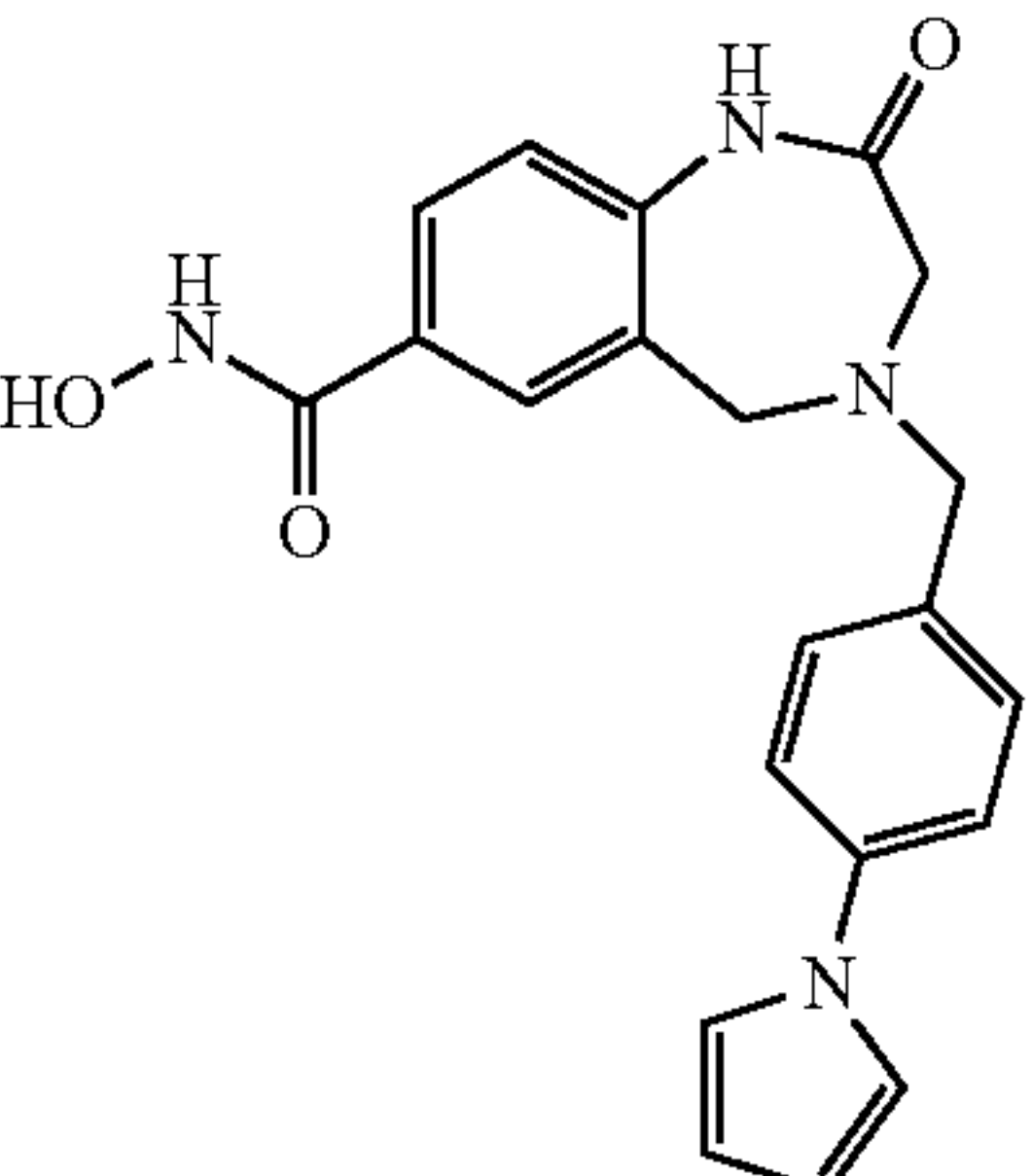
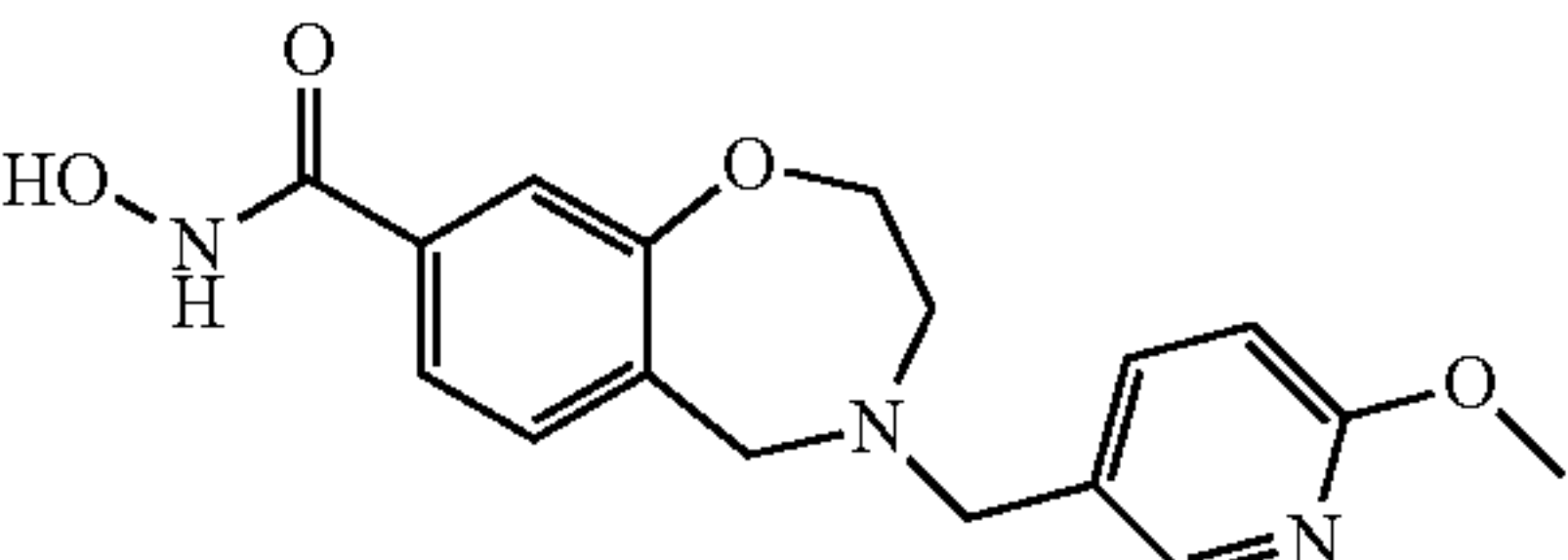
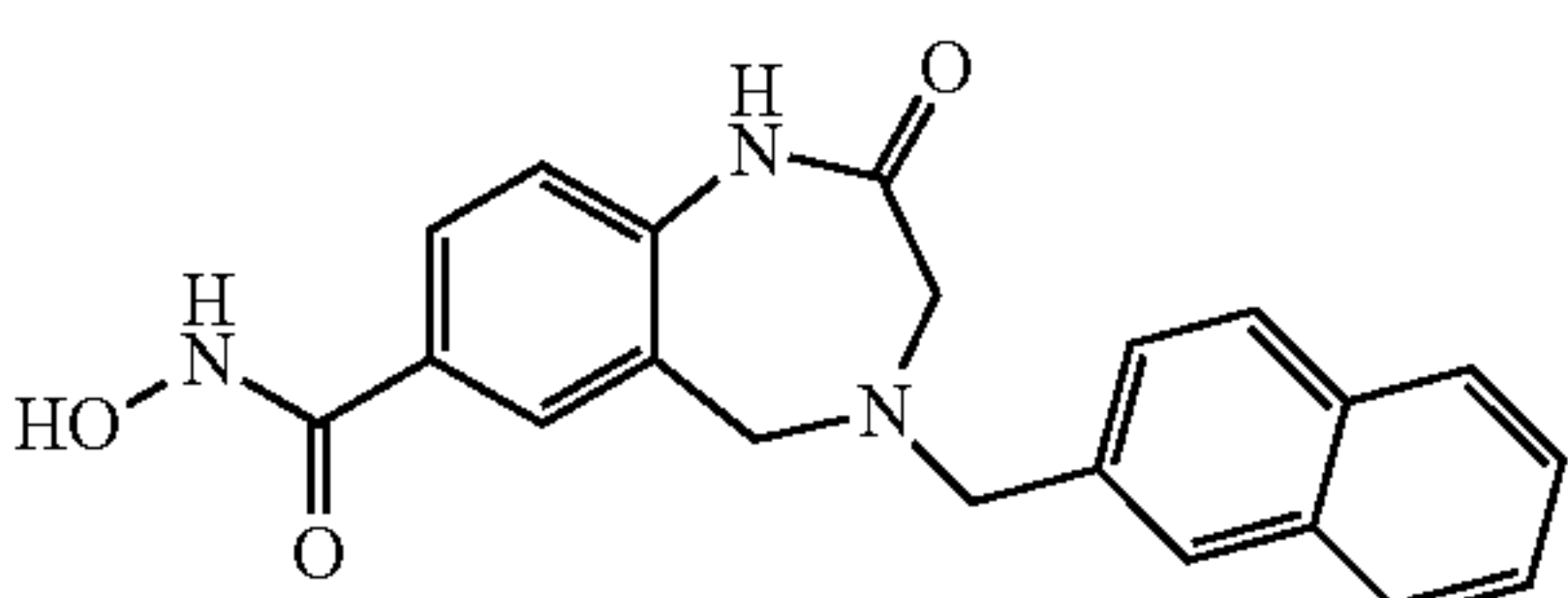
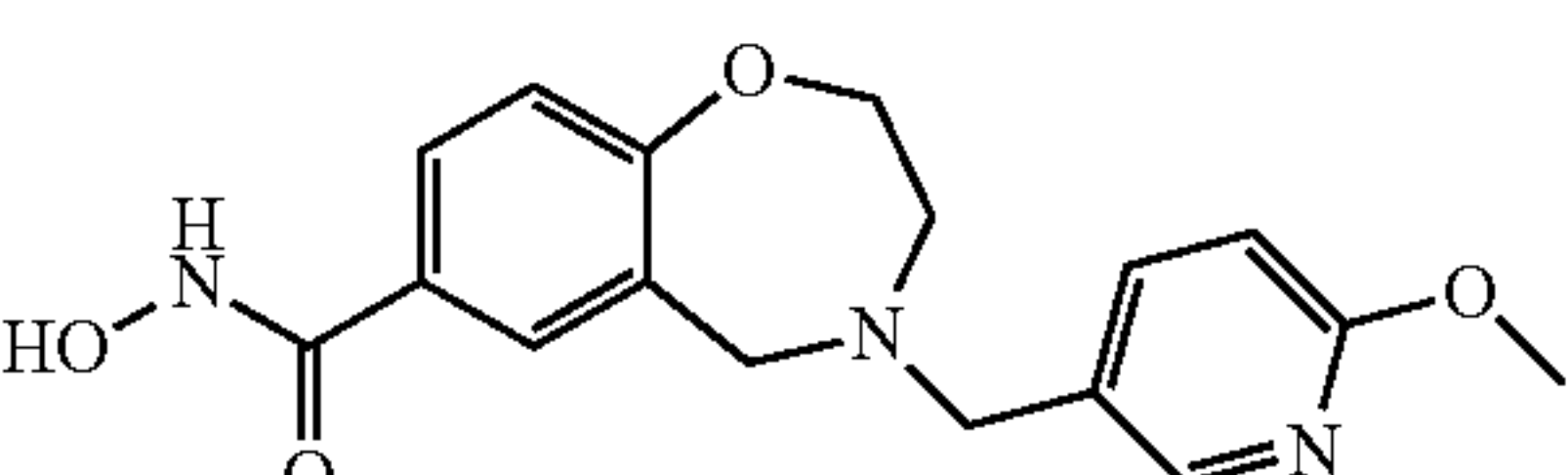
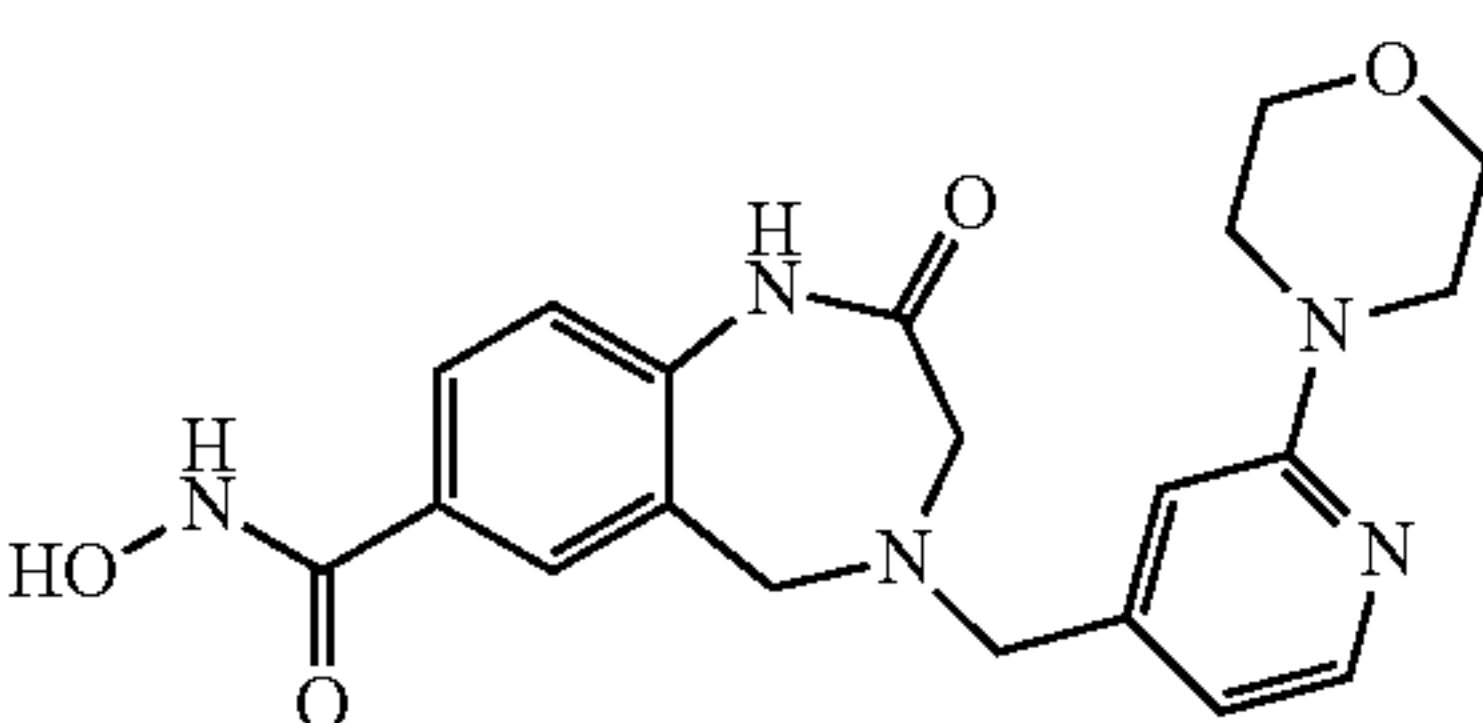
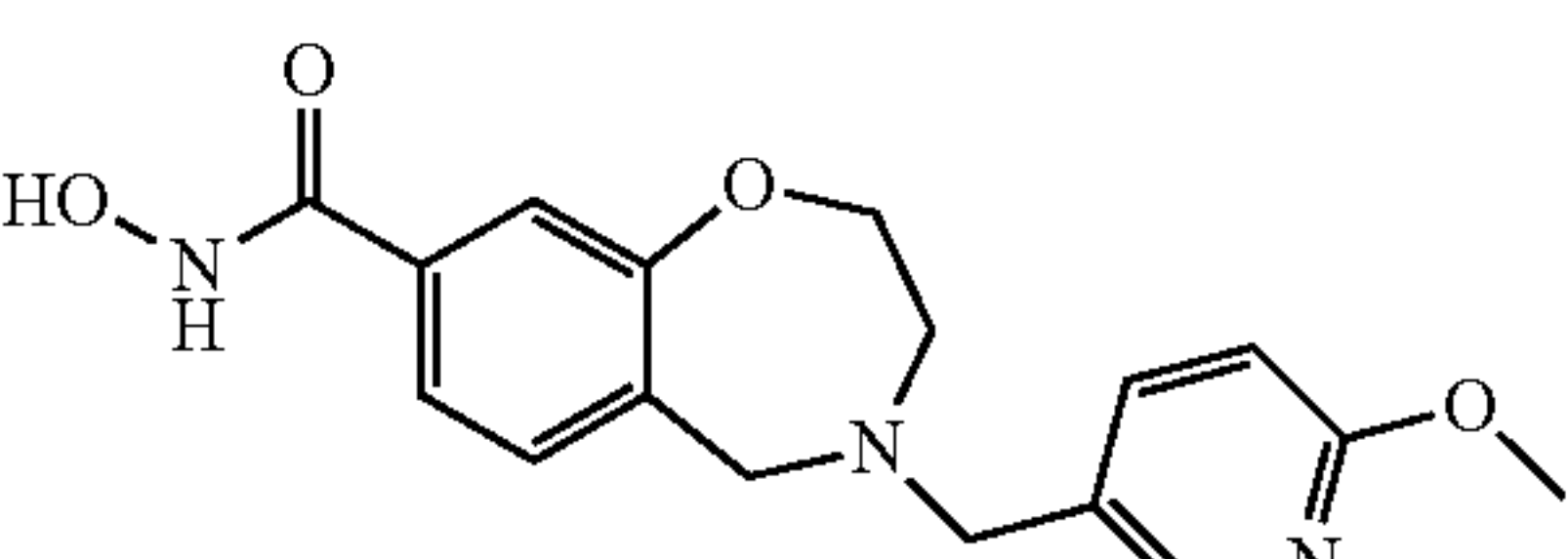
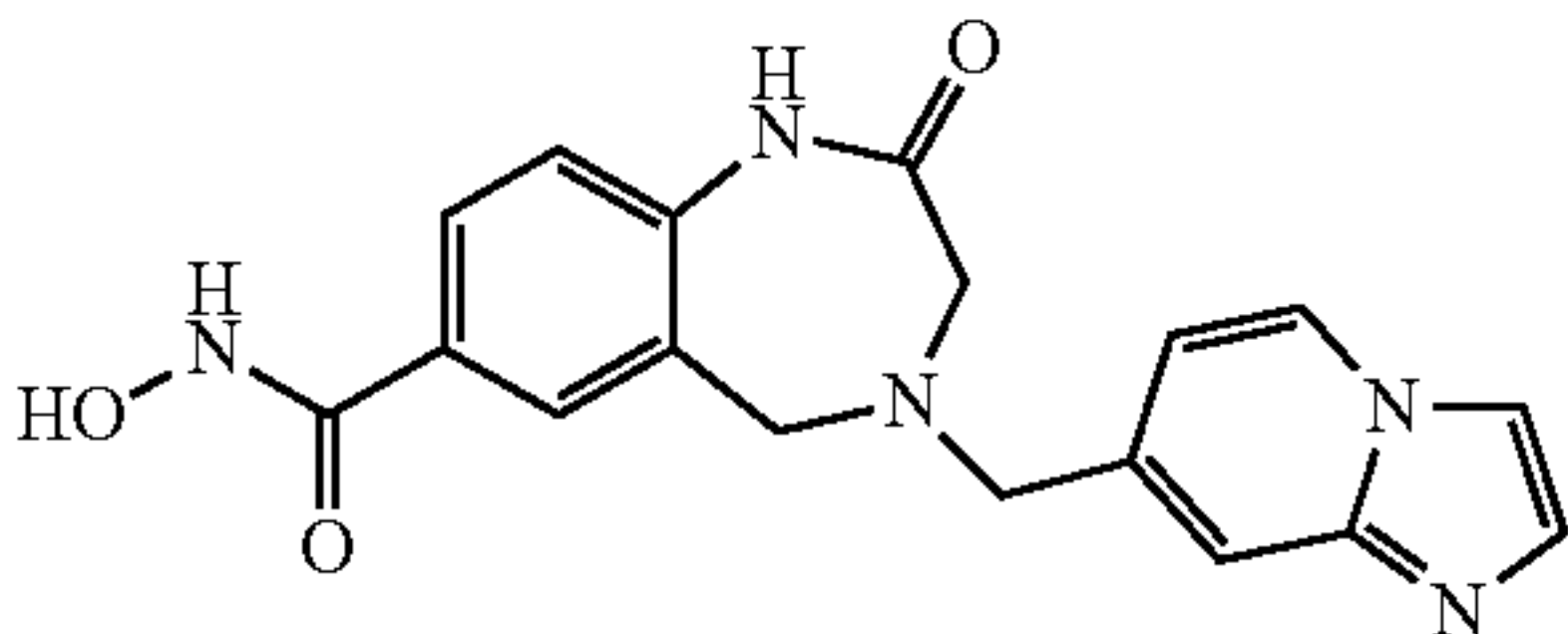
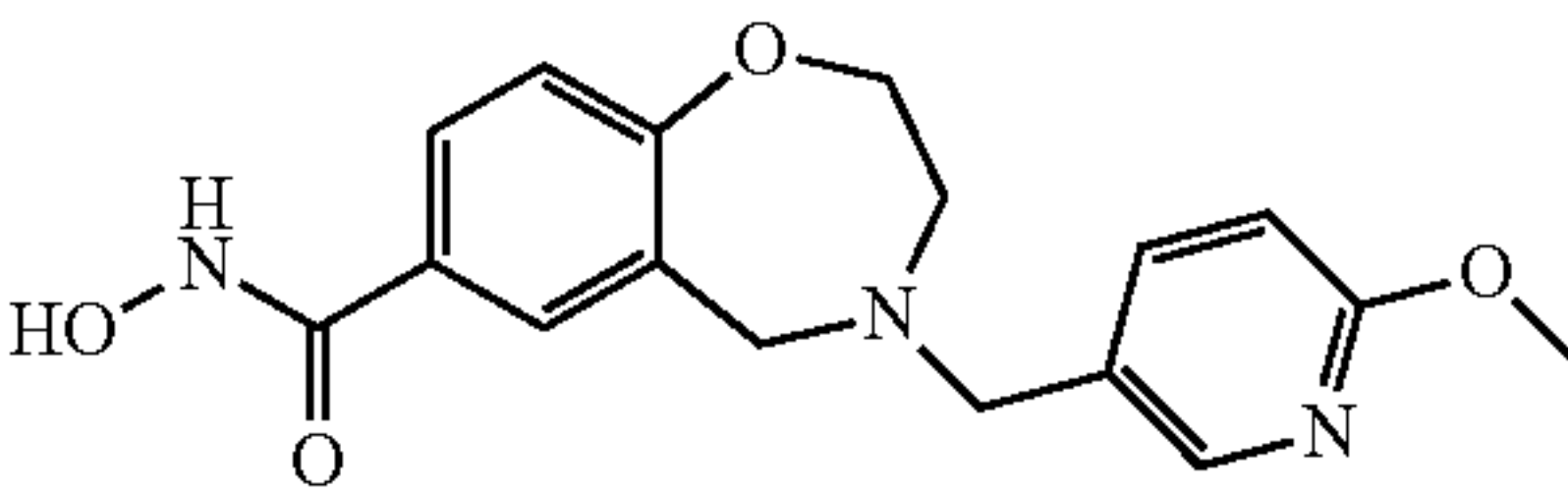
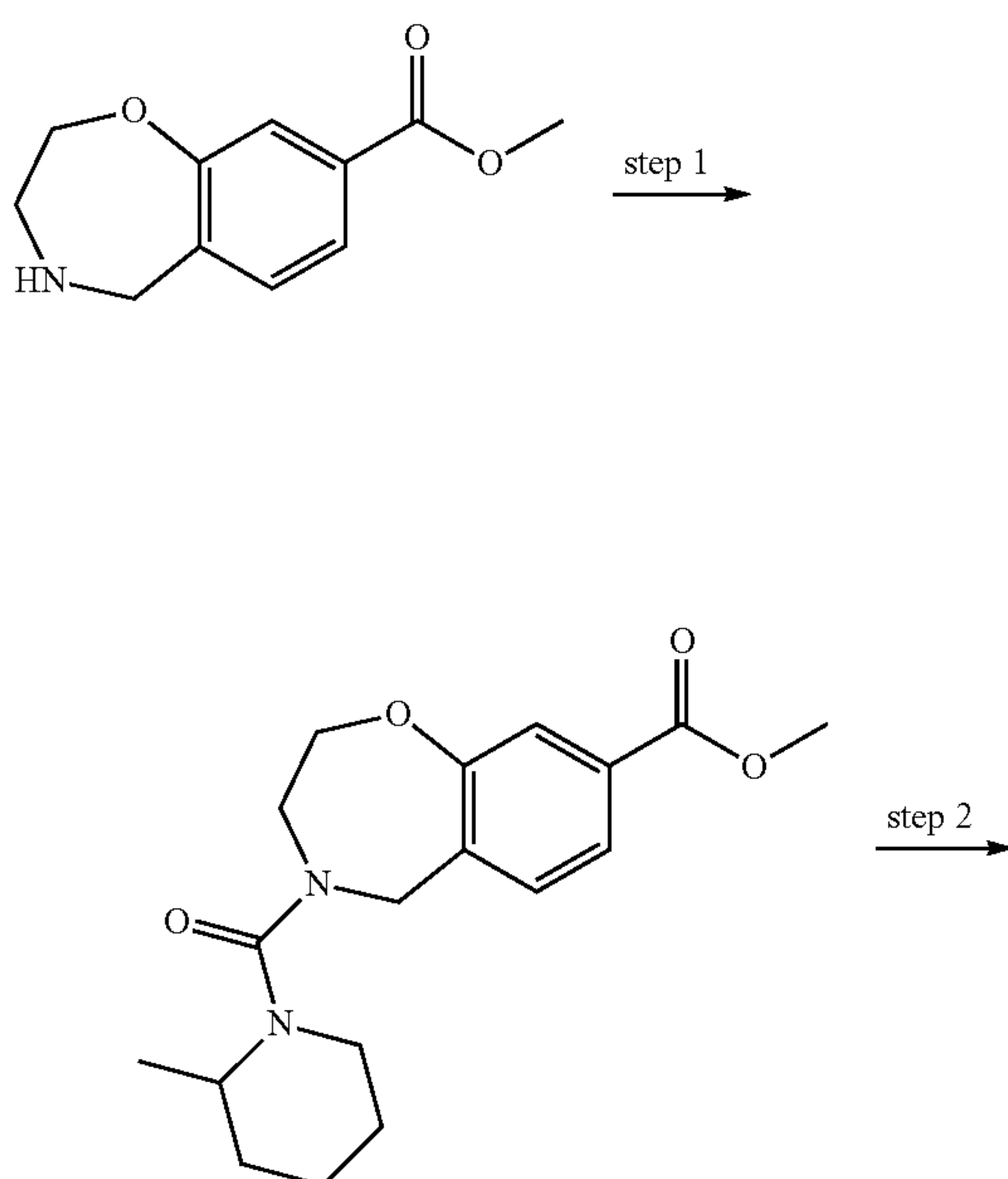
The following compounds were prepared by the parallel synthesis method of Example 84.			
Structure	Found M + H (ES)	Structure	Found M + H (ES)
	360		347
	346		346
	392		384
	361		395
	377		330
	362		330
	398		330

TABLE 40-continued

The following compounds were prepared by the parallel synthesis method of Example 84.			
Structure	Found M + H (ES)	Structure	Found M + H (ES)
	352		330

## Example 85

Preparation of N-hydroxy-4-(2-methylpiperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Step-1: Methyl 4-(2-methylpiperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

A 2-mL reaction vial was charged with triphosgene (0.1M in MeCN, 200  $\mu$ L, 20  $\mu$ mol), methyl 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (0.2 M in MeCN, 250  $\mu$ L, 50  $\mu$ mol) and triethylamine (neat, 14  $\mu$ L, 100  $\mu$ mol). The mixture was stirred for 20 min. To this mixture was then added 2-methylpiperidine (neat, 24.8 mg, 250  $\mu$ mol) and the resulting mixture was stirred at room temperature for 2 h, after which time it was diluted with sat aq  $\text{NaHCO}_3$  (500  $\mu$ L) and extracted with EtOAc (2 $\times$ 500  $\mu$ L). The combined organic layers were evaporated to dryness under reduced pressure.

Step-2: N-Hydroxy-4-(2-methylpiperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

Mixed solvent of THF/MeOH (3:1, 180  $\mu$ L) was added to the vial containing methyl 4-(2-methylpiperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate and it was shaken at 50° C. for 15 min to dissolve the residue.  $\text{NH}_2\text{OH}$  (50% in water, 125  $\mu$ L) was added followed by aq. 1N NaOH (85  $\mu$ L) and the vial was sealed and shaken at room temperature overnight. The solvent was evaporated under reduce pressure and the residue was dissolved in DMSO (500  $\mu$ L) then purified by HPLC to afford the title compound (7.1 mg, 42.6% yield). MS: (ES, m/z): 334  $[\text{M}+\text{H}]^+$ .



TABLE 41

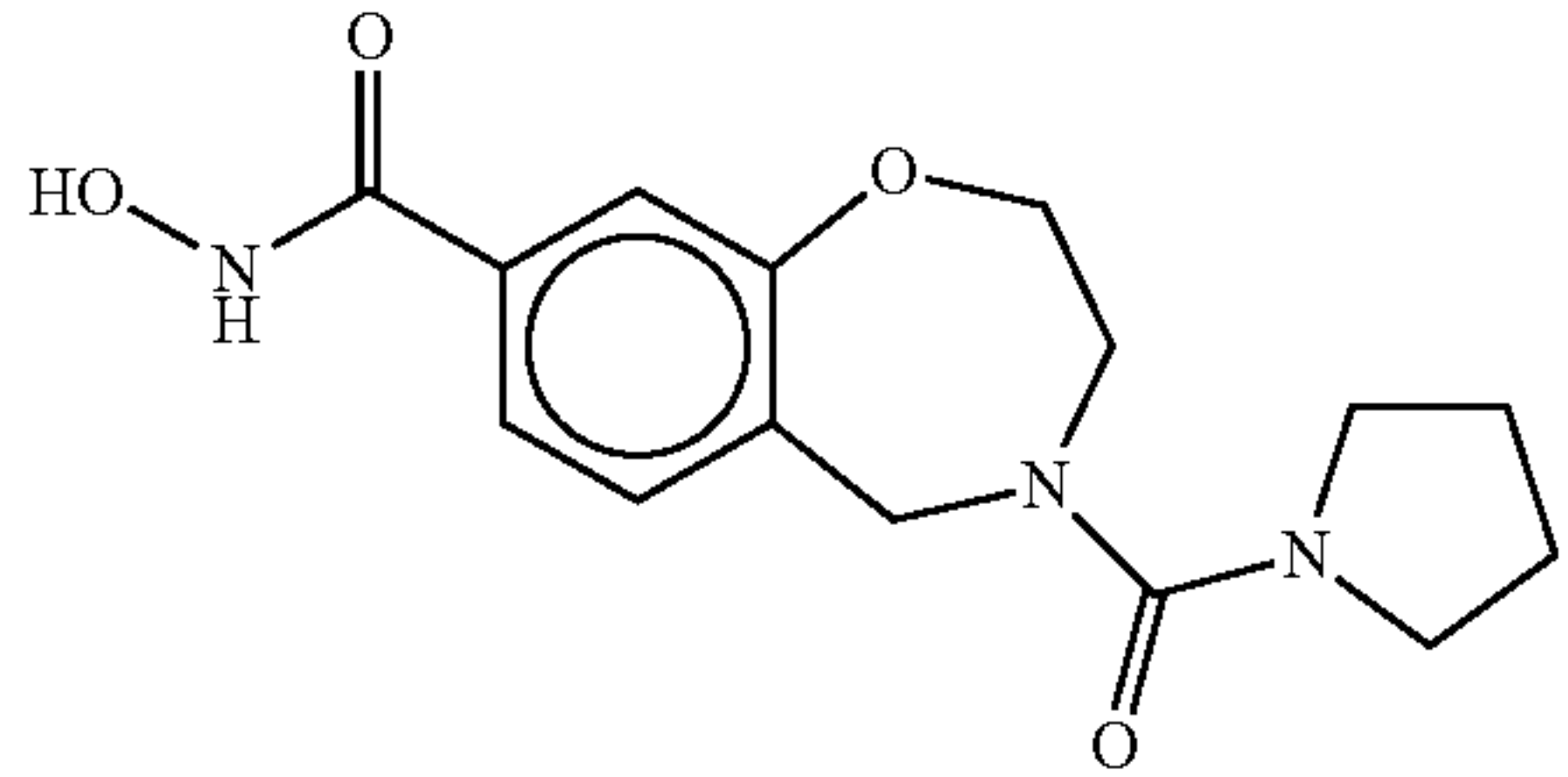
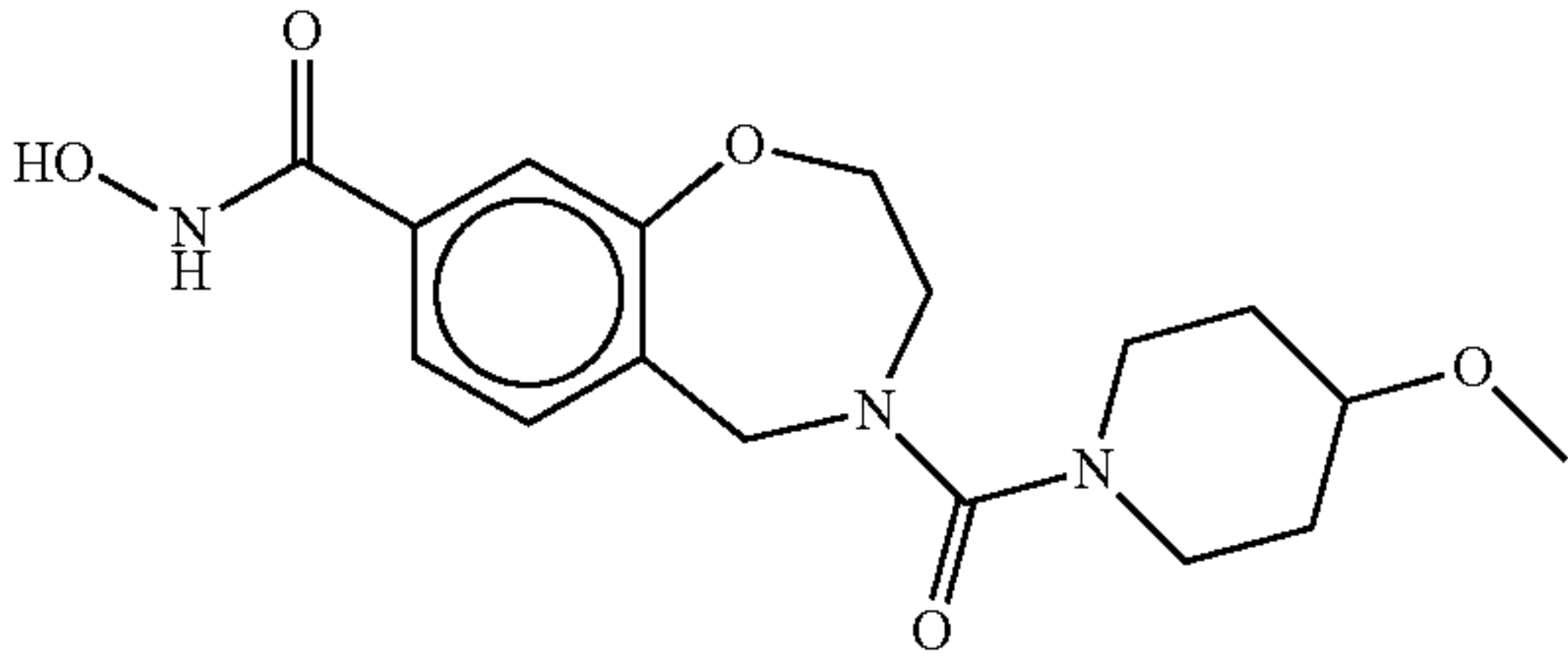
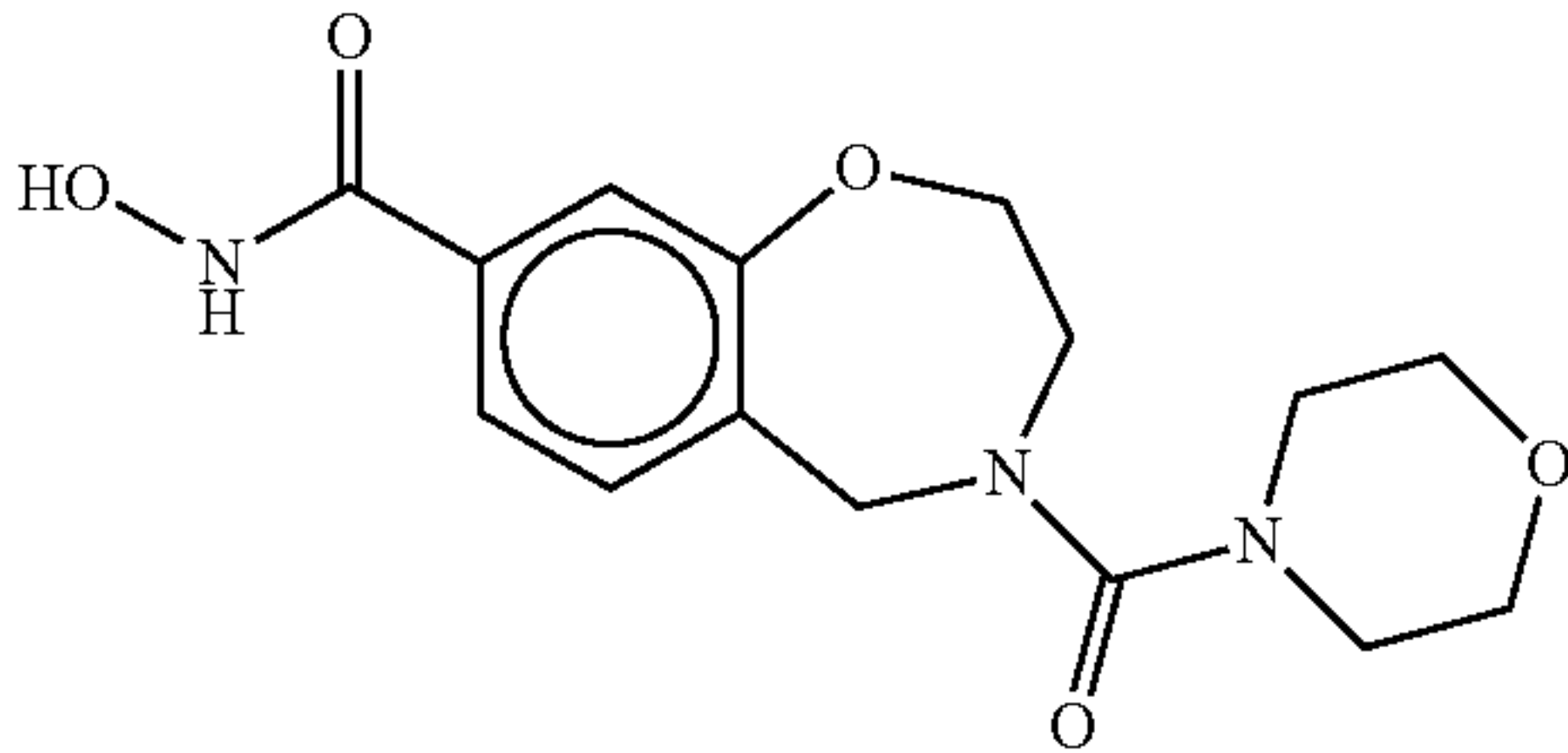
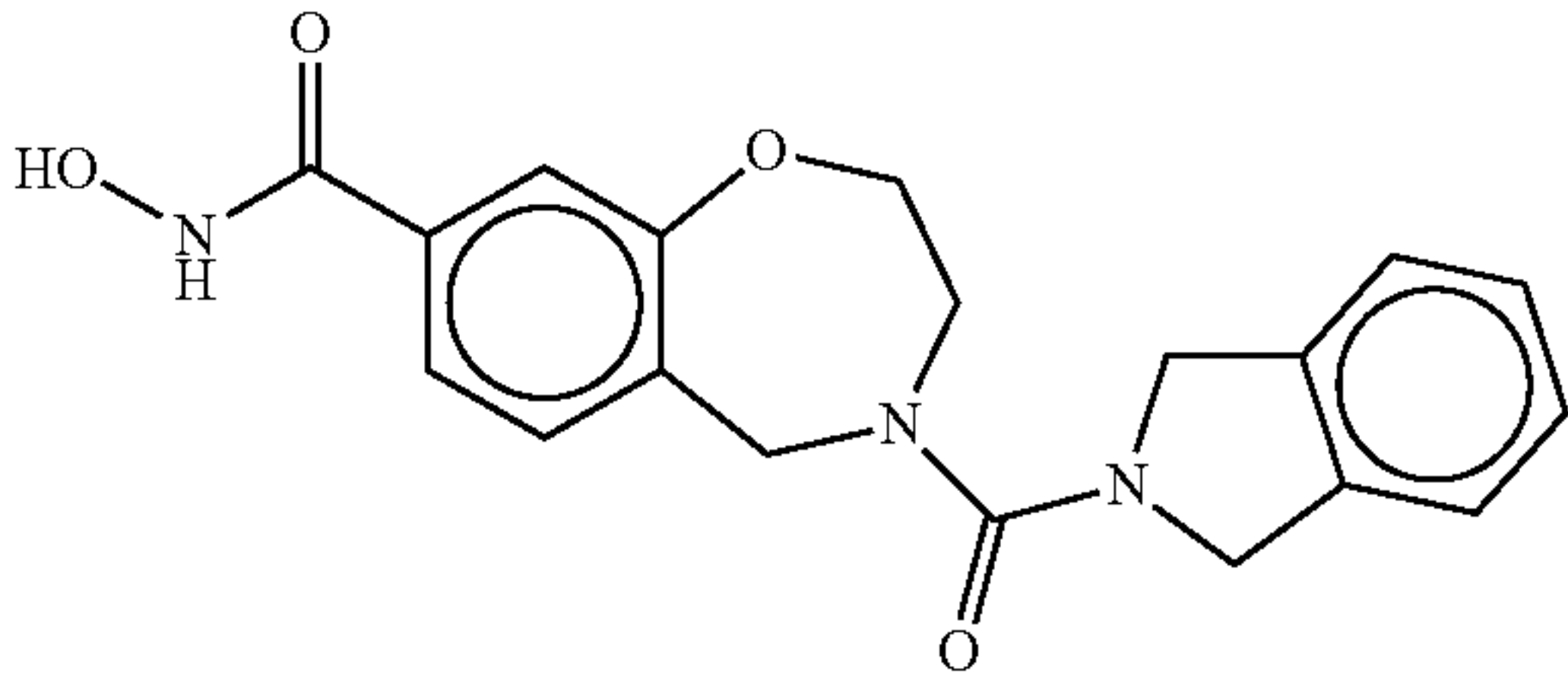
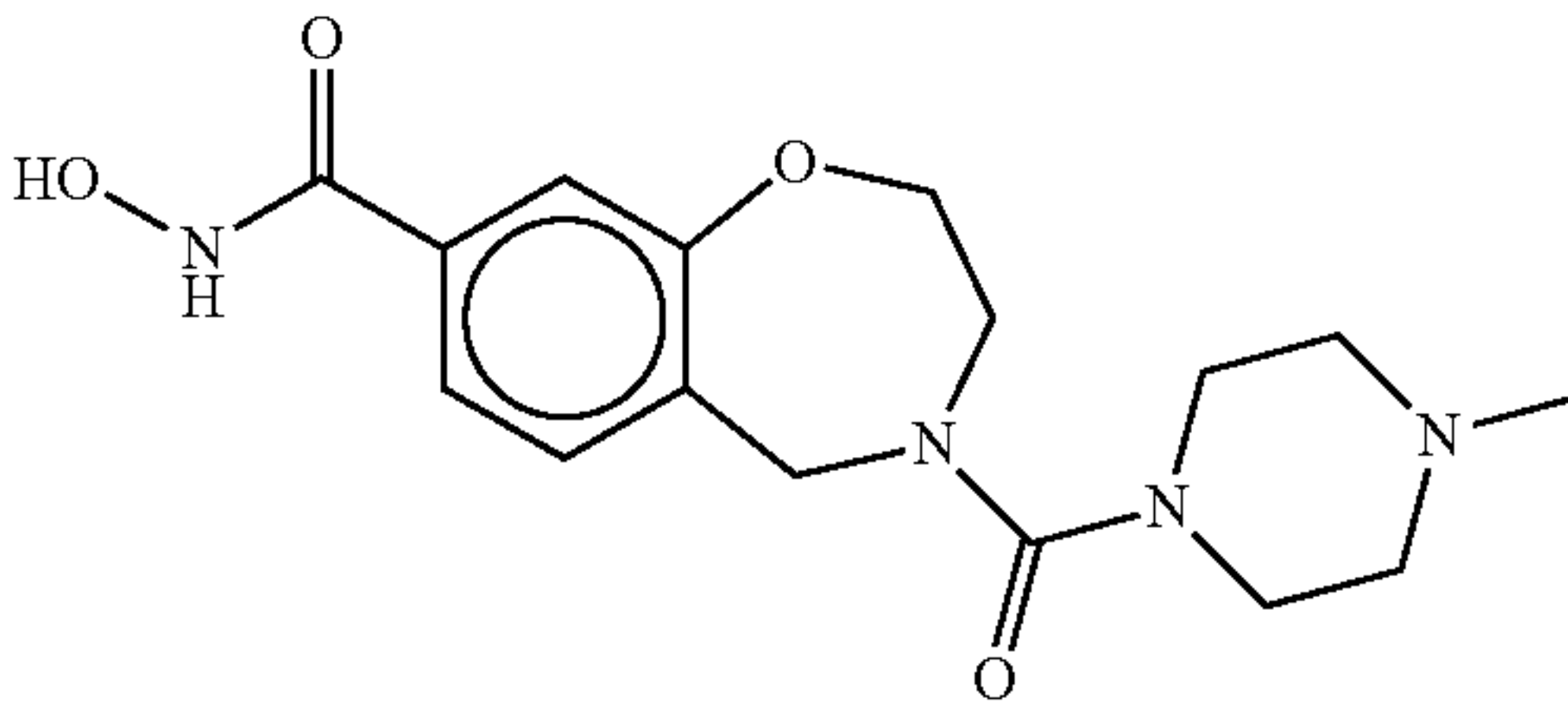
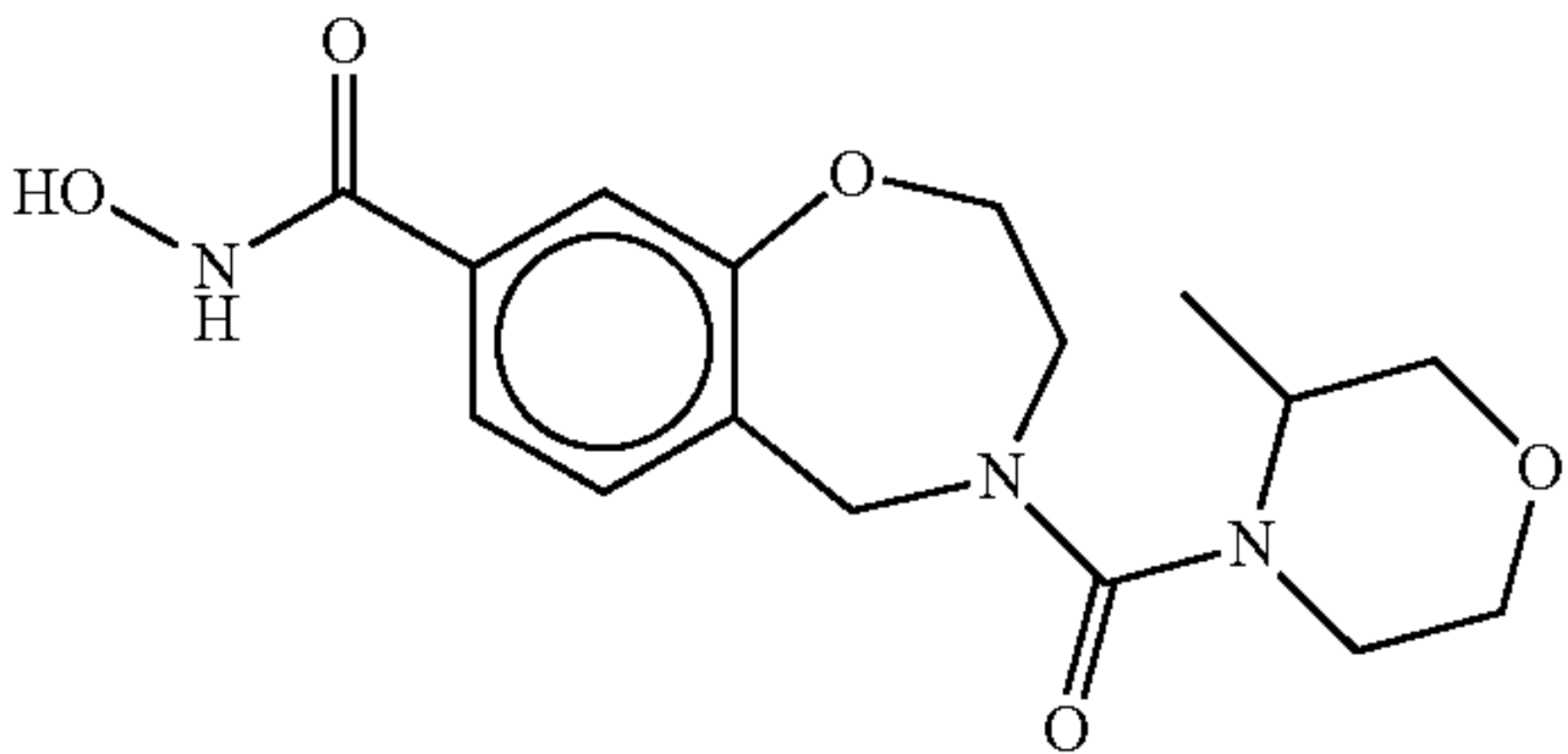
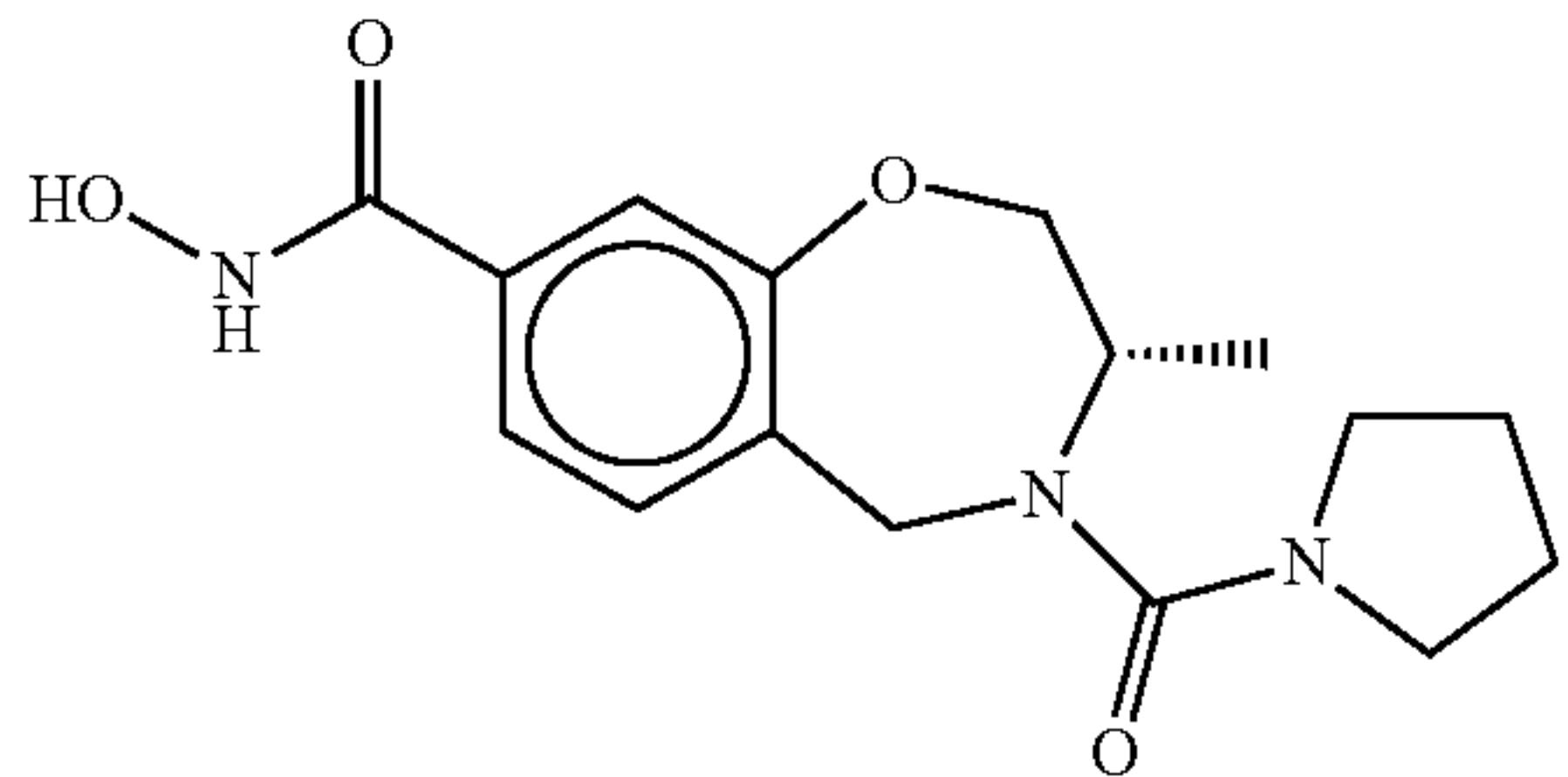
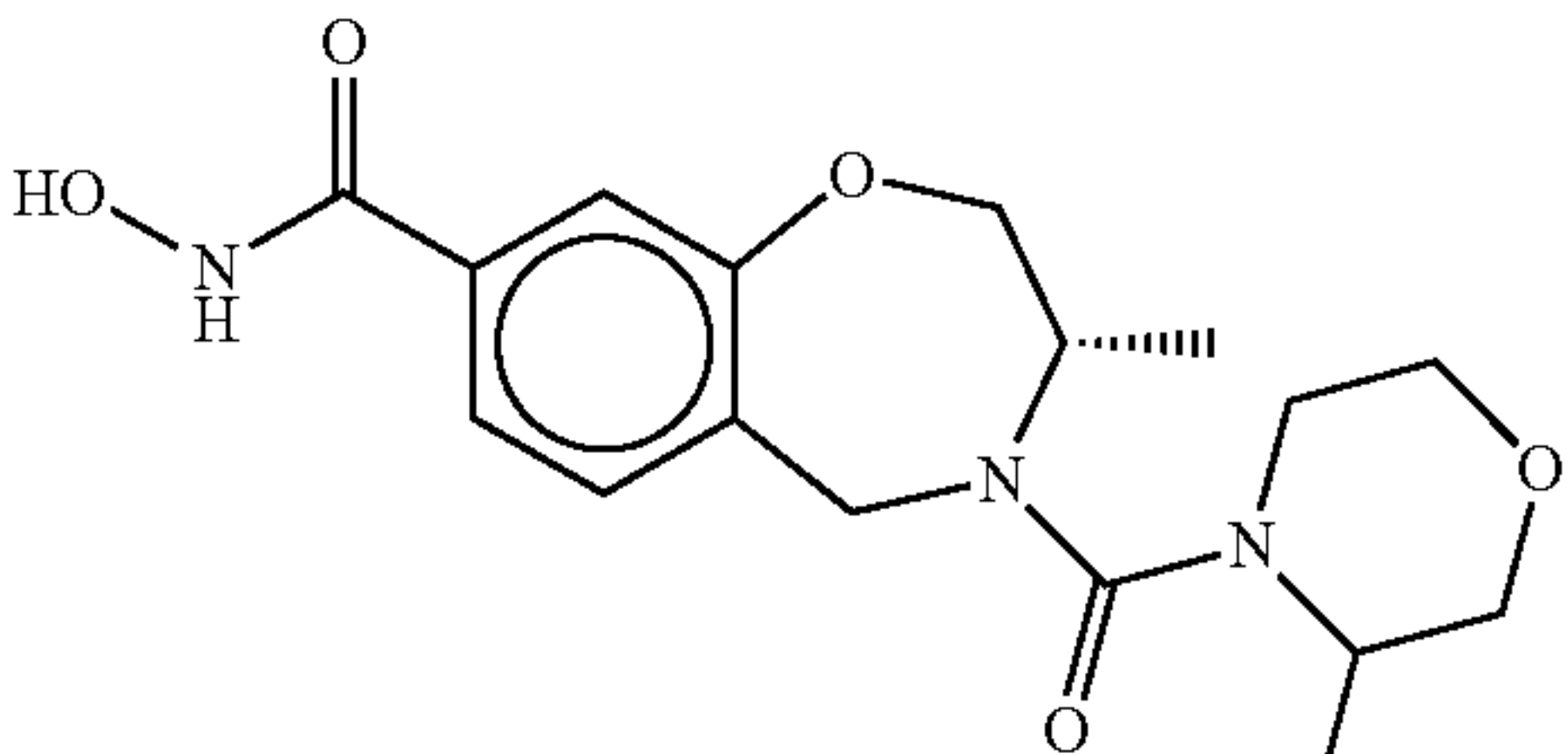
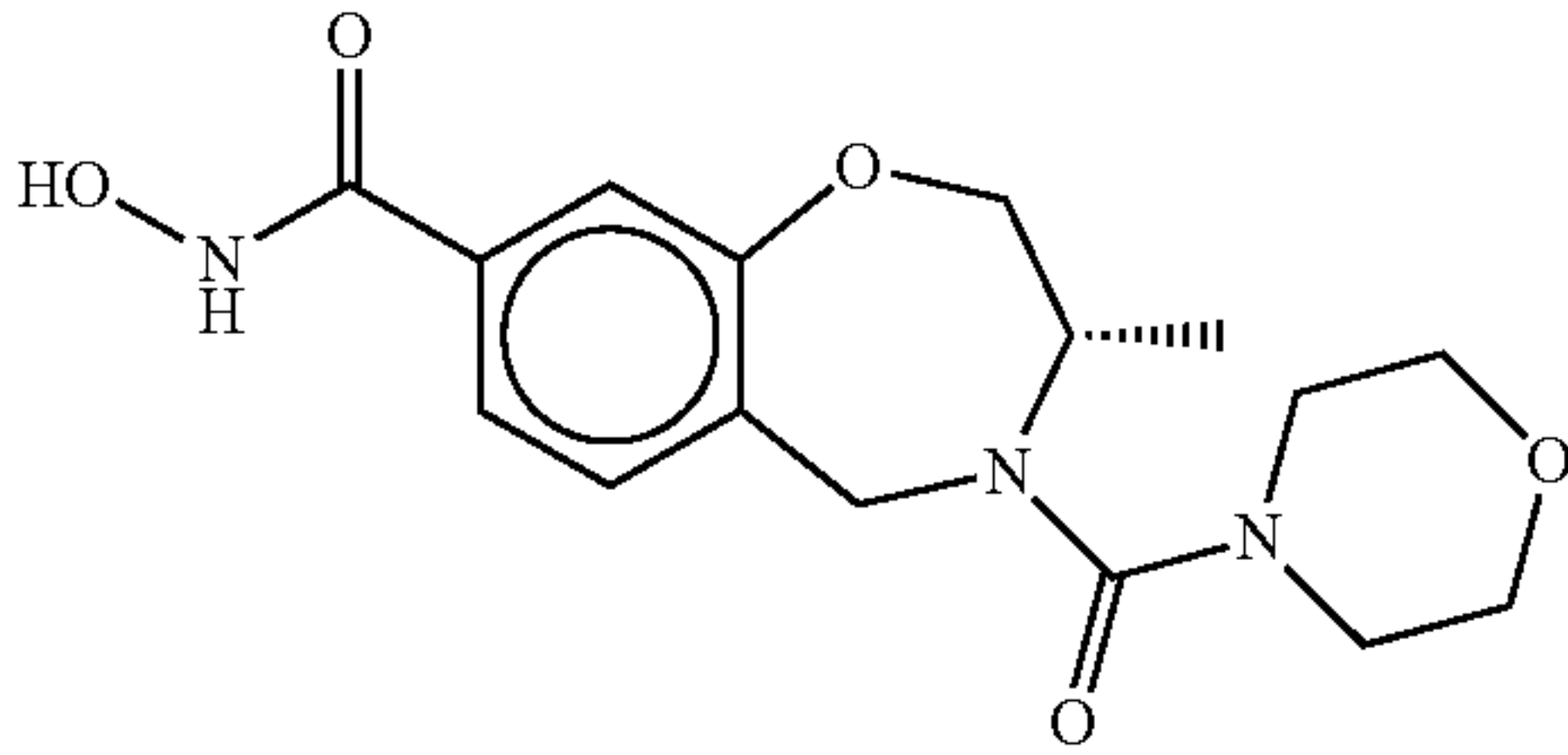
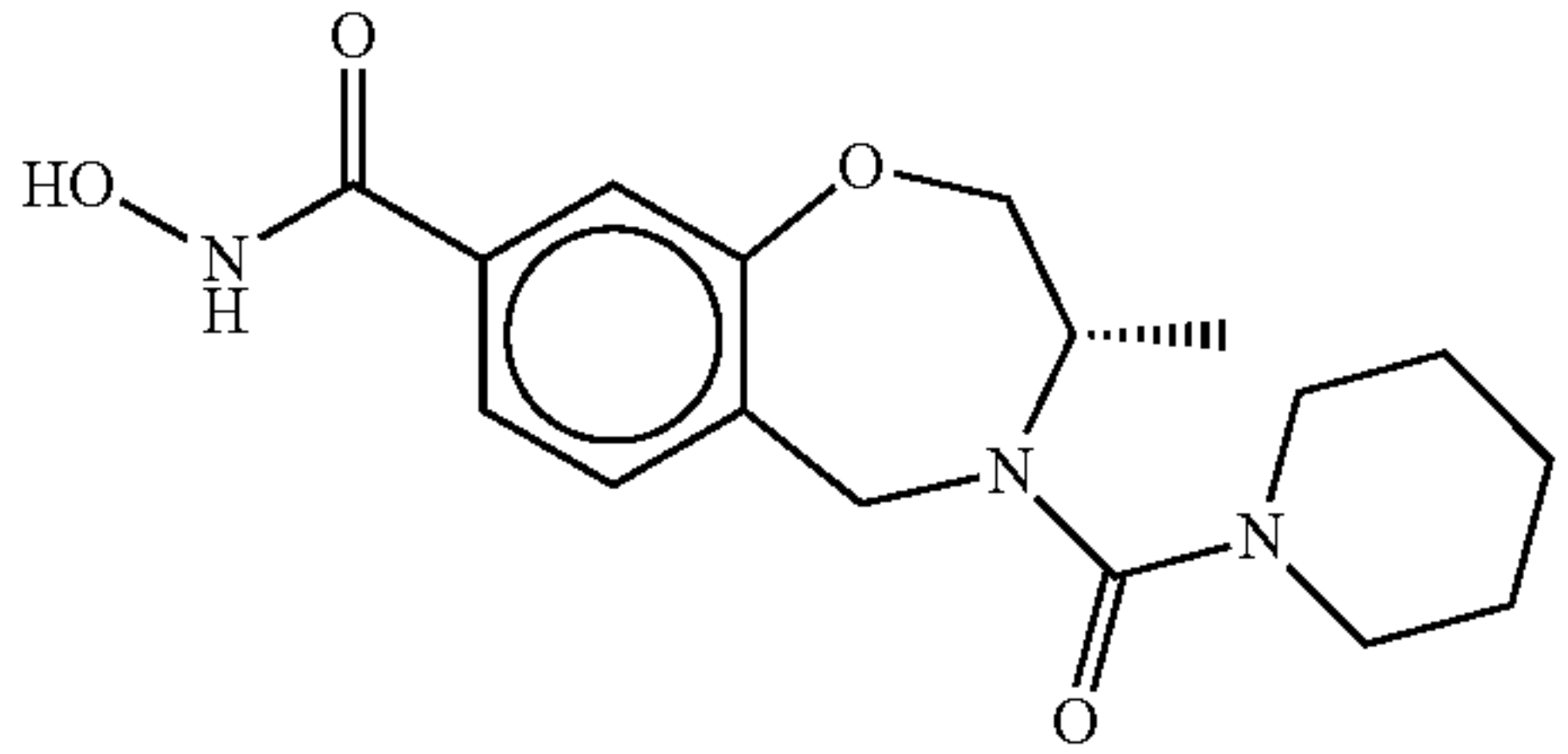
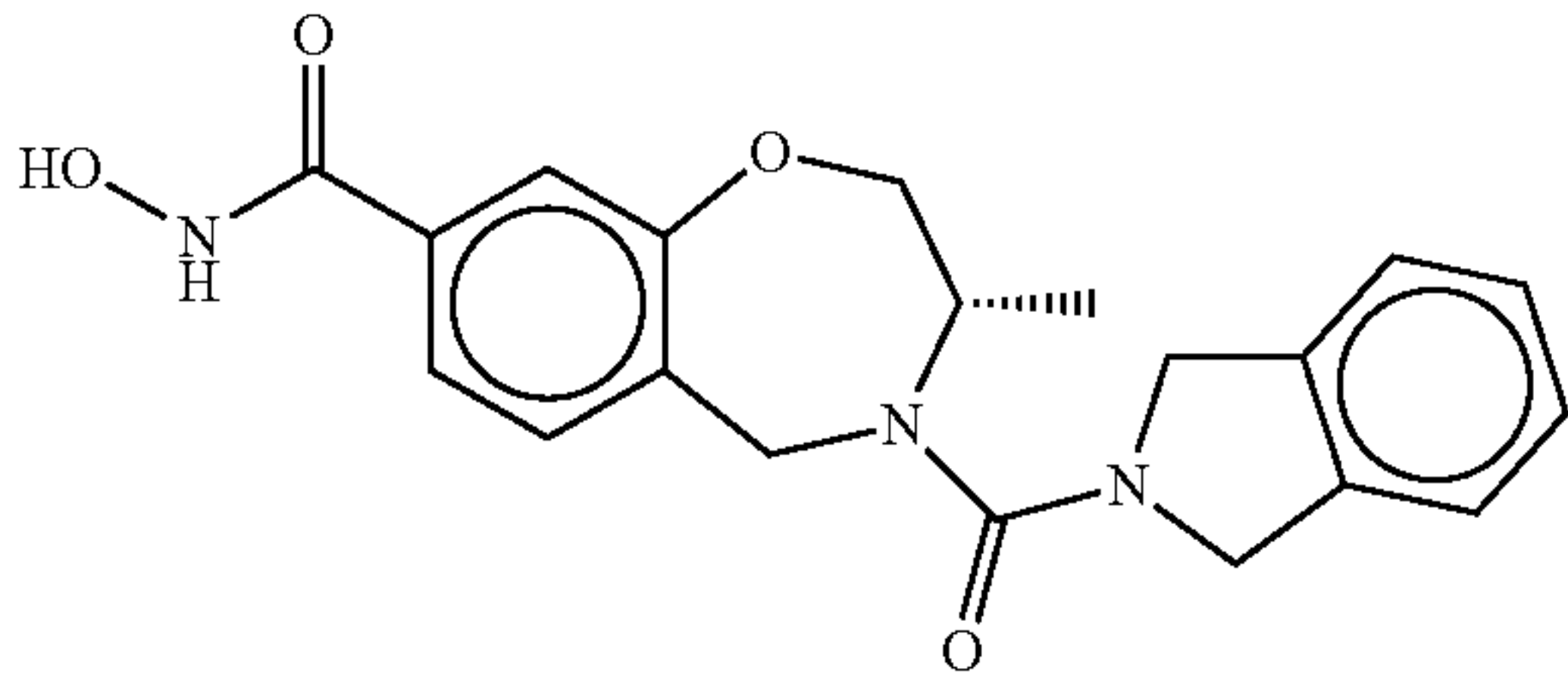
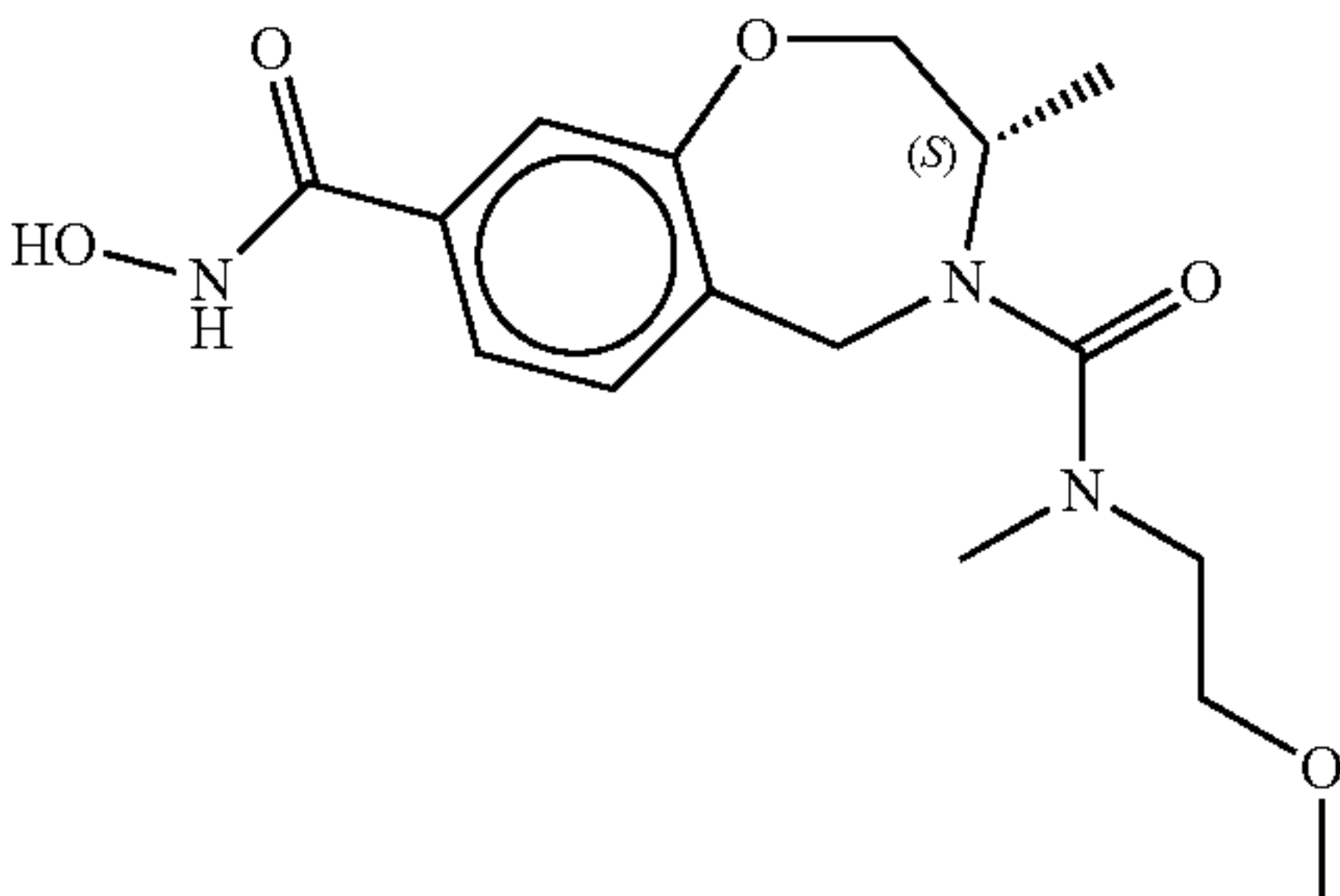
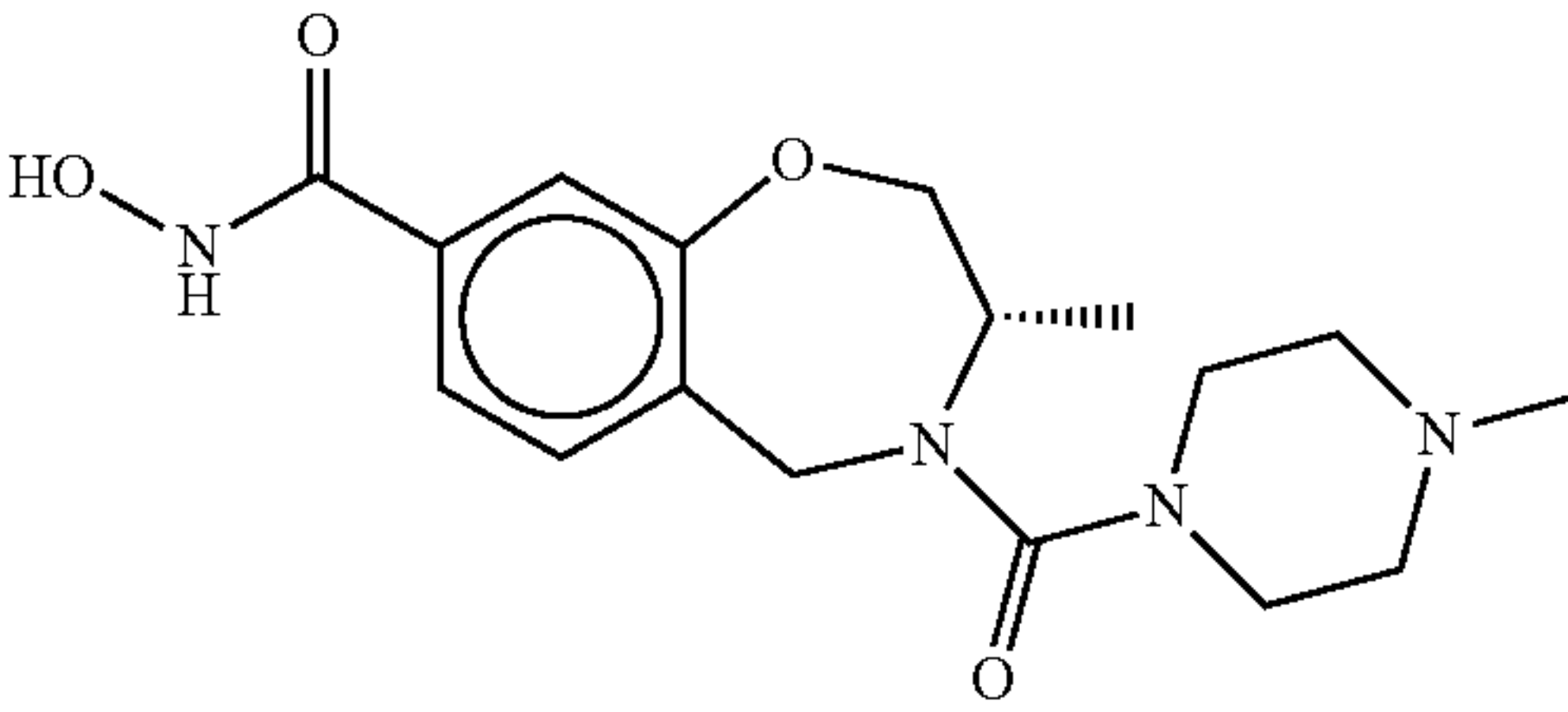
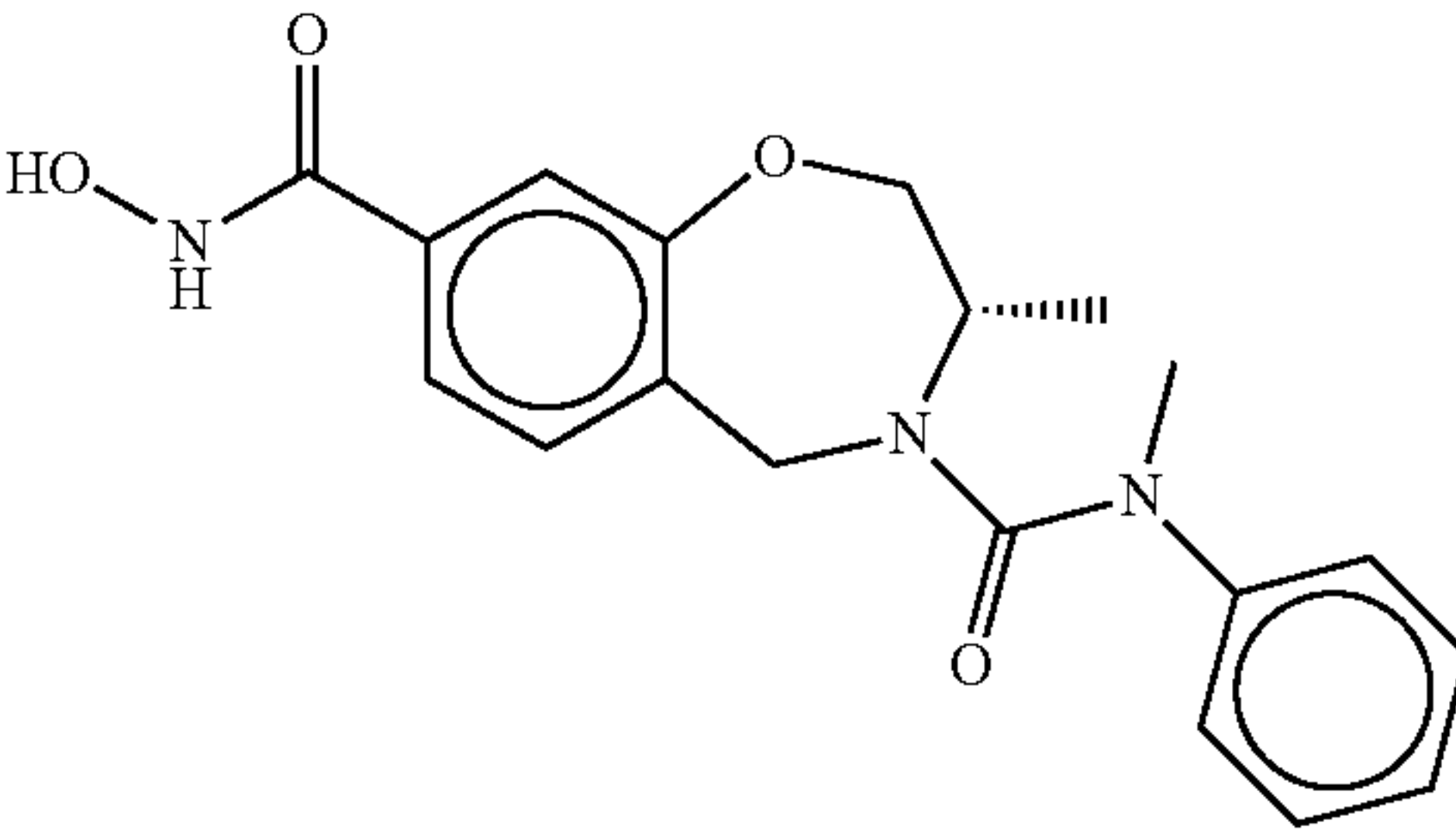
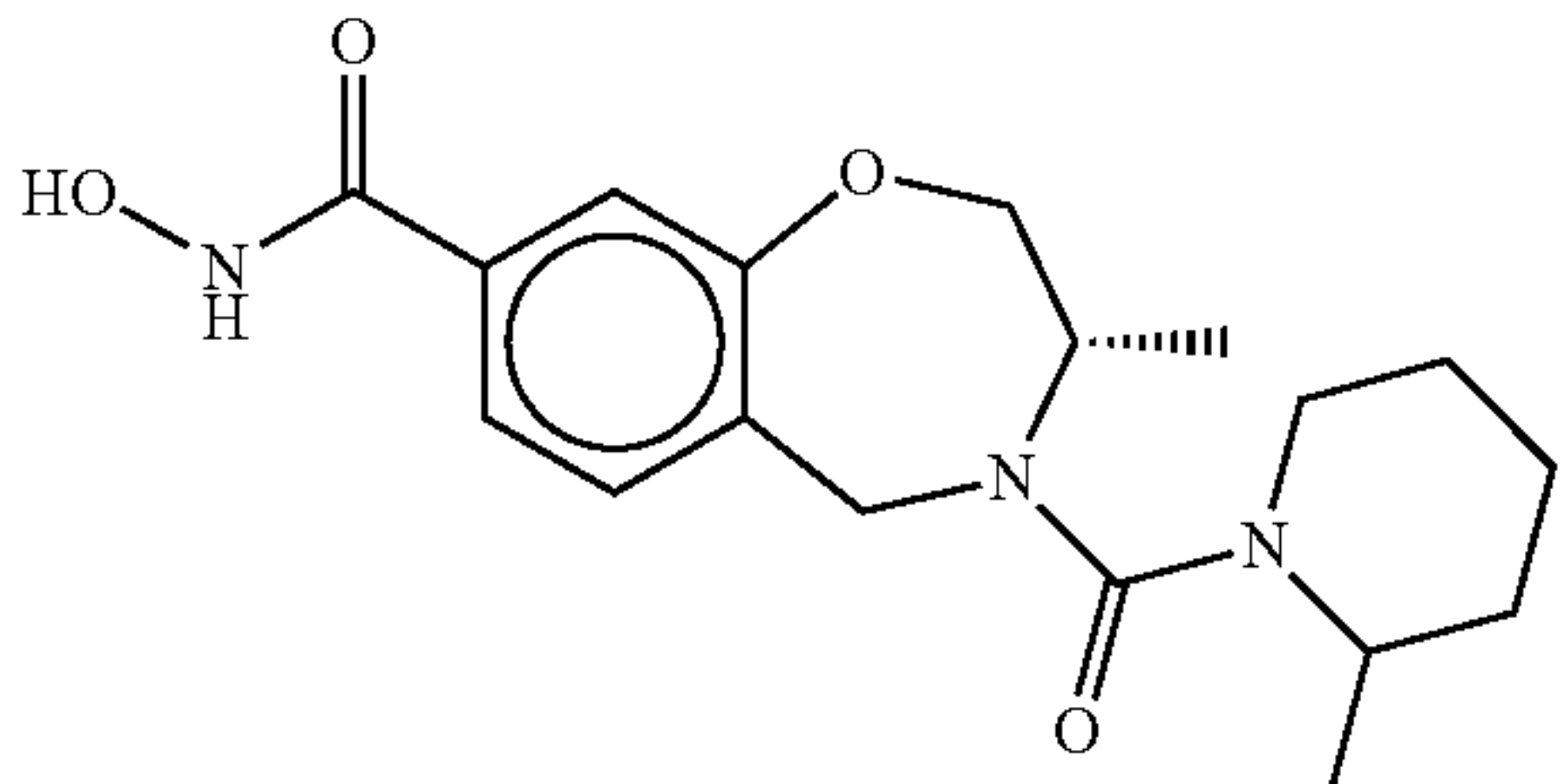
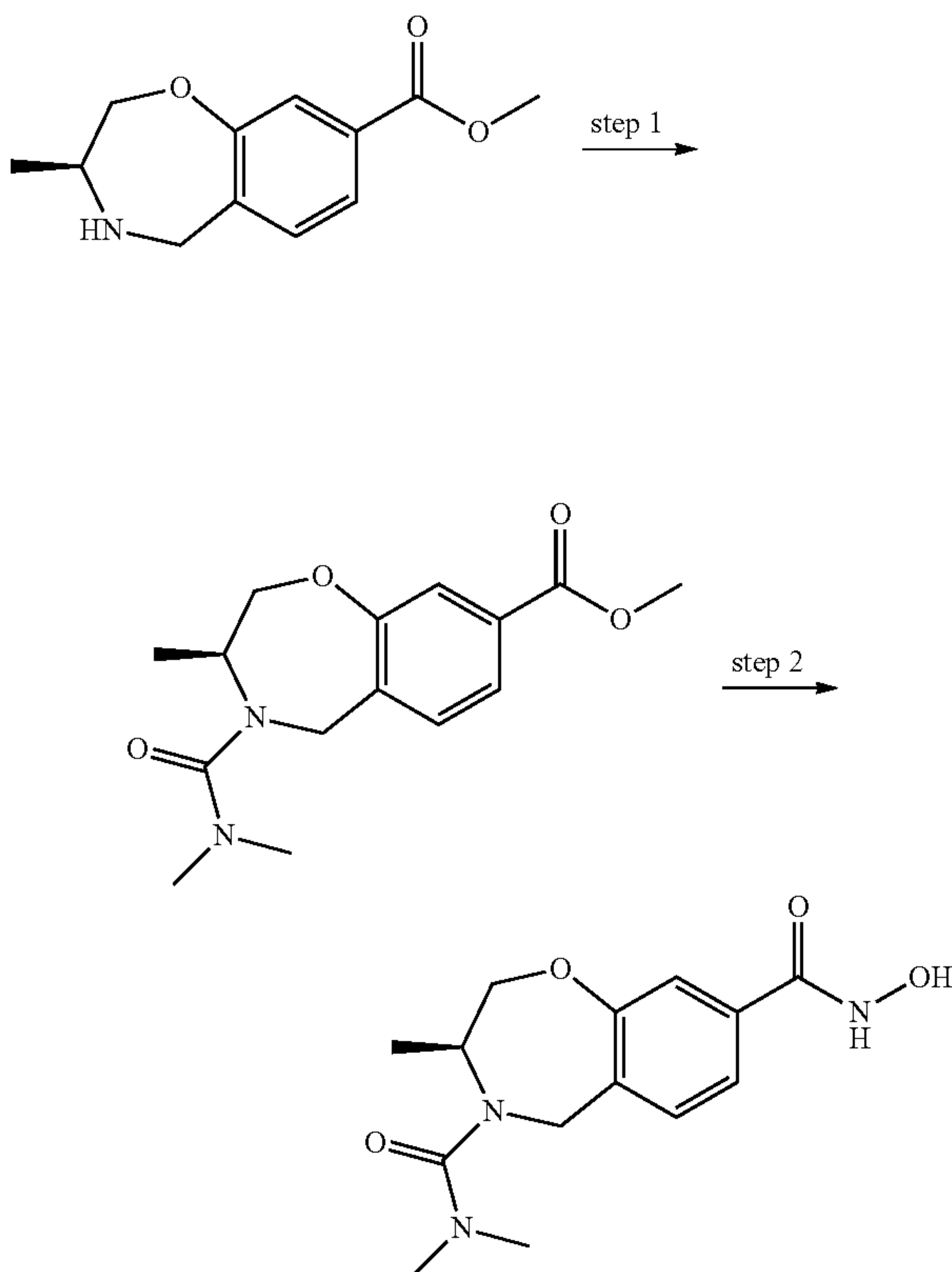
The following compounds were prepared by the parallel synthesis method of Example 85.			
Structure	Found M + H (ES)	Structure	Found M + H (ES)
	306		350
	322		354
	335		336
	320		350
	336		334
	368		338

TABLE 41-continued

The following compounds were prepared by the parallel synthesis method of Example 85.			
Structure	Found M + H (ES)	Structure	Found M + H (ES)
	349		356
	348		

## Example 86

Preparation of (S)—N8-hydroxy-N4,N4,3-trimethyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide



Step-1: Methyl (S)-4-(dimethylcarbamoyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

30

A 2-mL reaction vial was charged with dimethylcarbamic chloride (0.2M in dichloroethane, 400  $\mu$ L, 80  $\mu$ mol), methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (0.2M in dichloroethane, 200  $\mu$ L, 40  $\mu$ mol) and triethylamine (neat, 11  $\mu$ L, 80  $\mu$ mol). The reaction was stirred at room temperature for 2 h, after which time it was diluted with brine (500  $\mu$ L) and extracted with EtOAc (2 $\times$ 500  $\mu$ L). The combined organic layers were evaporated to dryness under reduced pressure.

35

40

45

Step-2: (S)—N8-hydroxy-N4,N4,3-trimethyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide

50

Mixed solvent of THF/MeOH (3:1, 180  $\mu$ L) was added to the vial containing methyl (S)-4-(dimethylcarbamoyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate and it was shaken at 50° C. for 15 min to dissolve the residue.  $\text{NH}_2\text{OH}$  (50% in water, 125  $\mu$ L) was added followed by aq. 1N NaOH (85  $\mu$ L) and the vial was sealed and shaken at room temperature overnight. The solvent was evaporated under reduce pressure and the residue was dissolved in DMSO (500  $\mu$ L) then purified by HPLC to afford the title compound. MS: (ES, m/z): 294 [M+H]<sup>+</sup>.

55

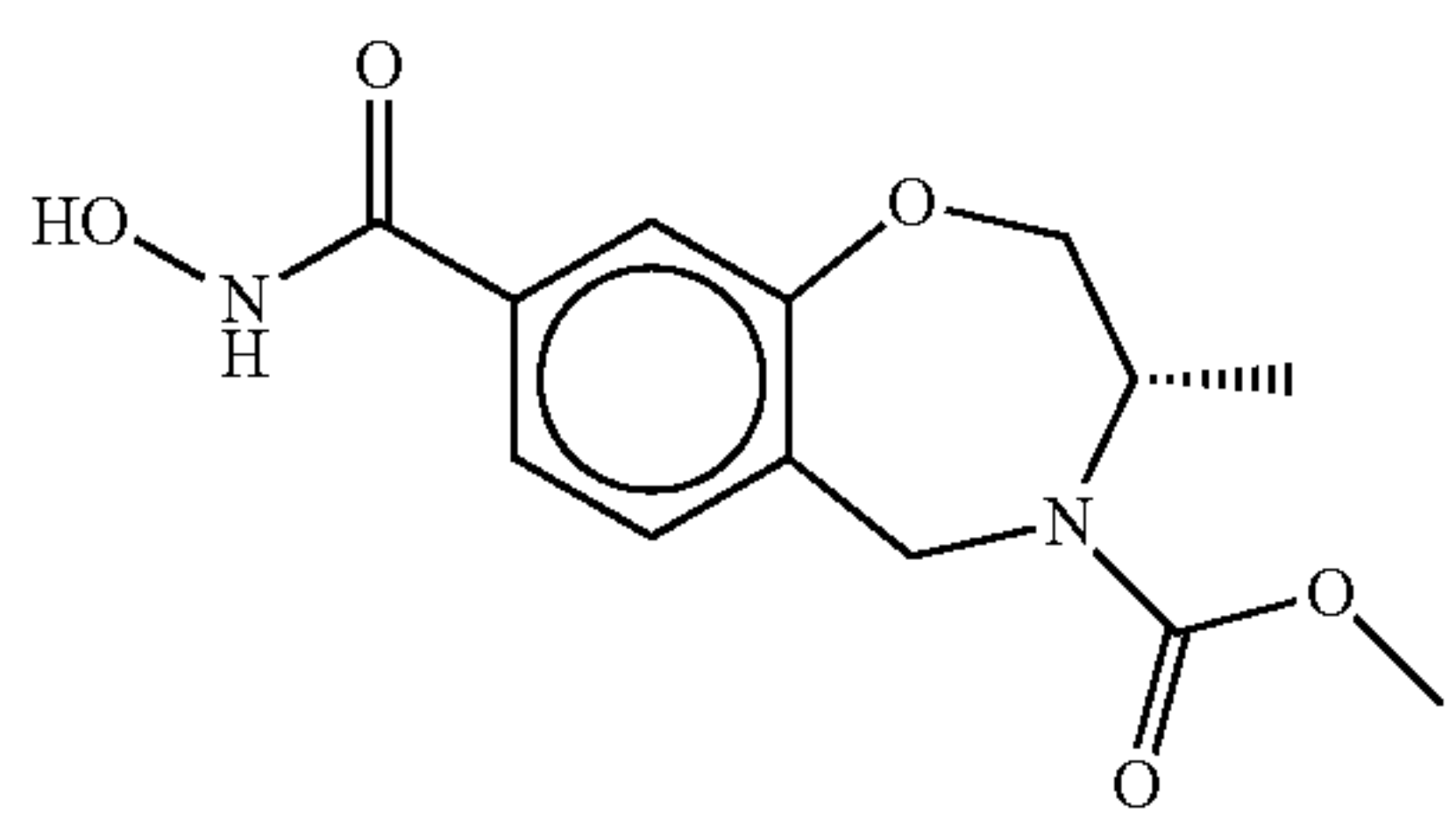
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65



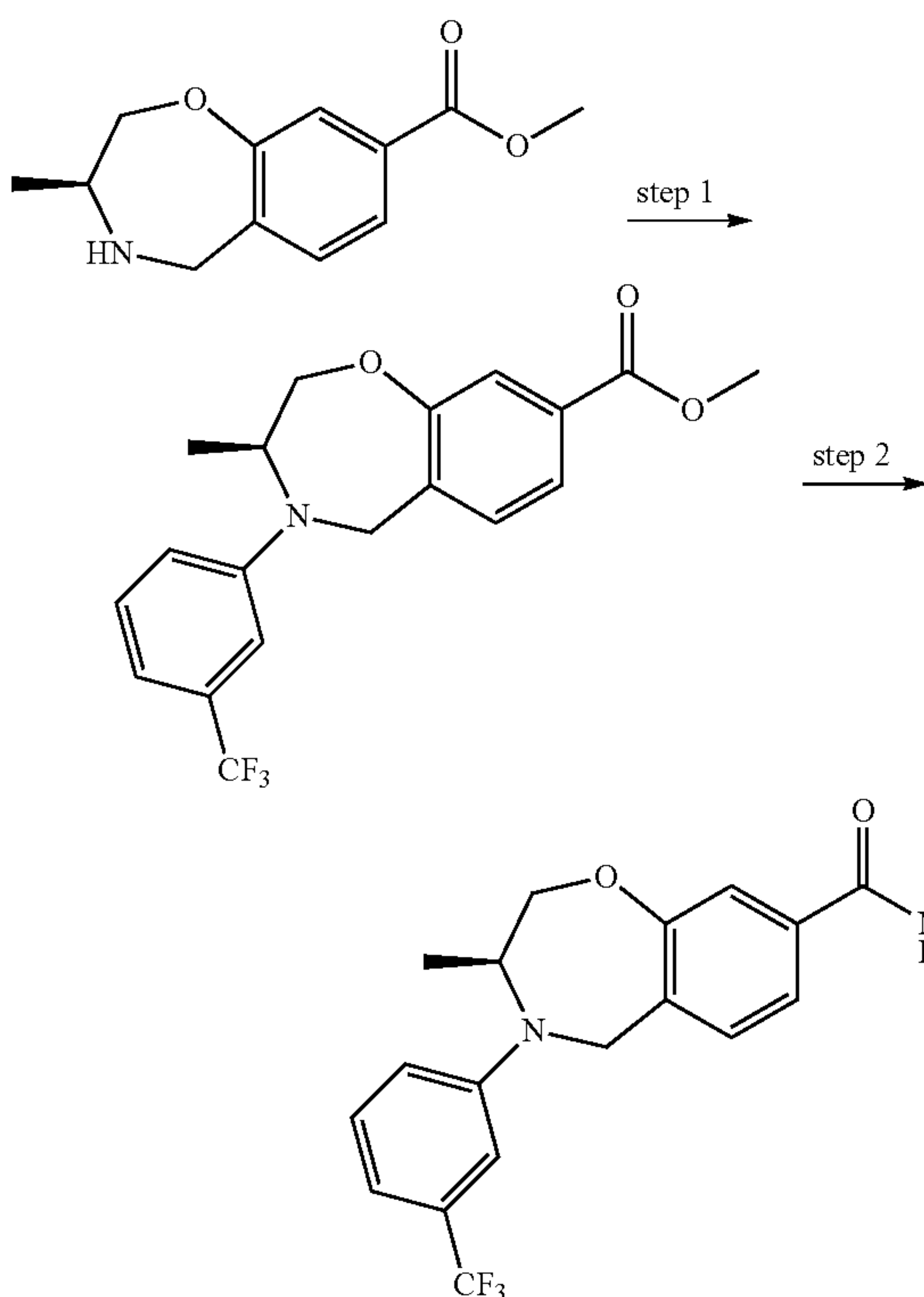
255

TABLE 42

The following compound was prepared by the parallel synthesis method of Example 86.	
Structure	Found M + H (ES)
	281

## Example 87

Preparation of (S)—N-hydroxy-3-methyl-4-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



Step-1: Methyl (S)-3-methyl-4-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

A 2-mL reaction vial was charged with dimethylcarbamic chloride (0.2M in dichloroethane, 400  $\mu$ L, 80  $\mu$ mol), methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (0.2M in dichloroethane, 150  $\mu$ L, 30  $\mu$ mol), triethylamine (neat, 12.5  $\mu$ L, 90  $\mu$ mol), Cu(OAc)<sub>2</sub> (150  $\mu$ L 0.4M in DMSO, 60  $\mu$ mol), and (3-(trifluoromethyl)phenyl)boronic acid (300  $\mu$ L, 0.2M in dichloroethane, 60  $\mu$ mol). The

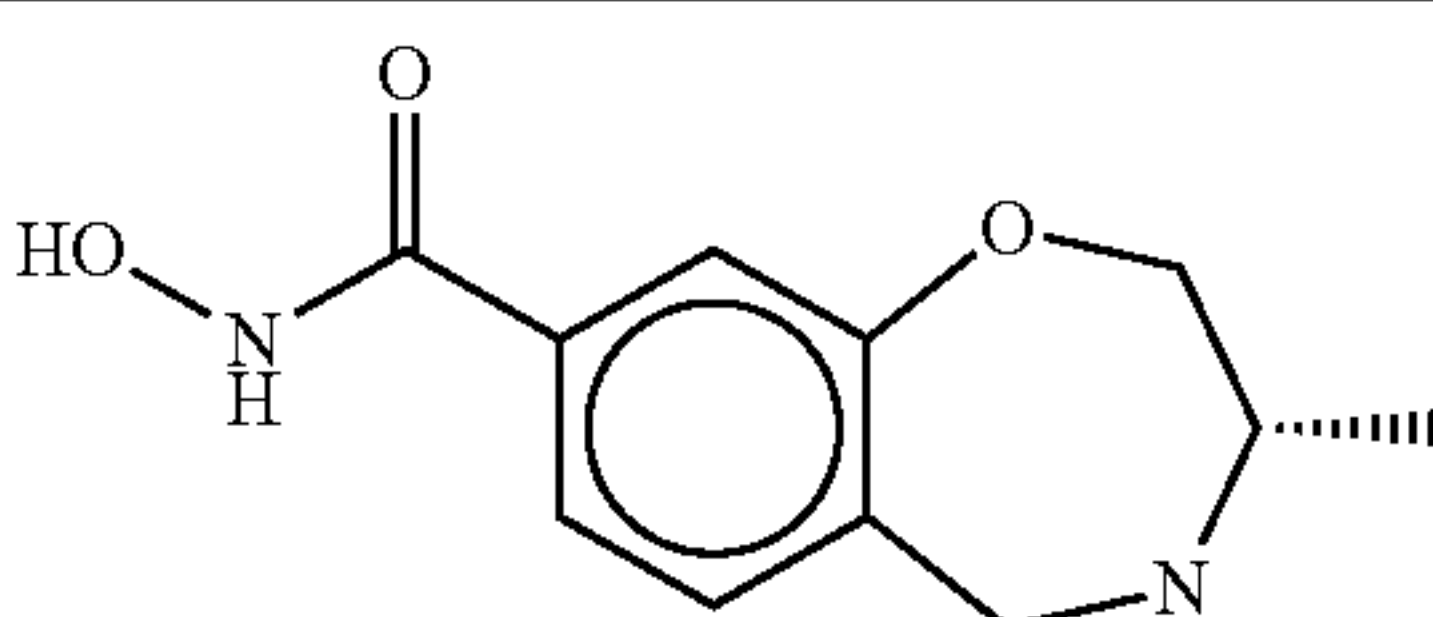

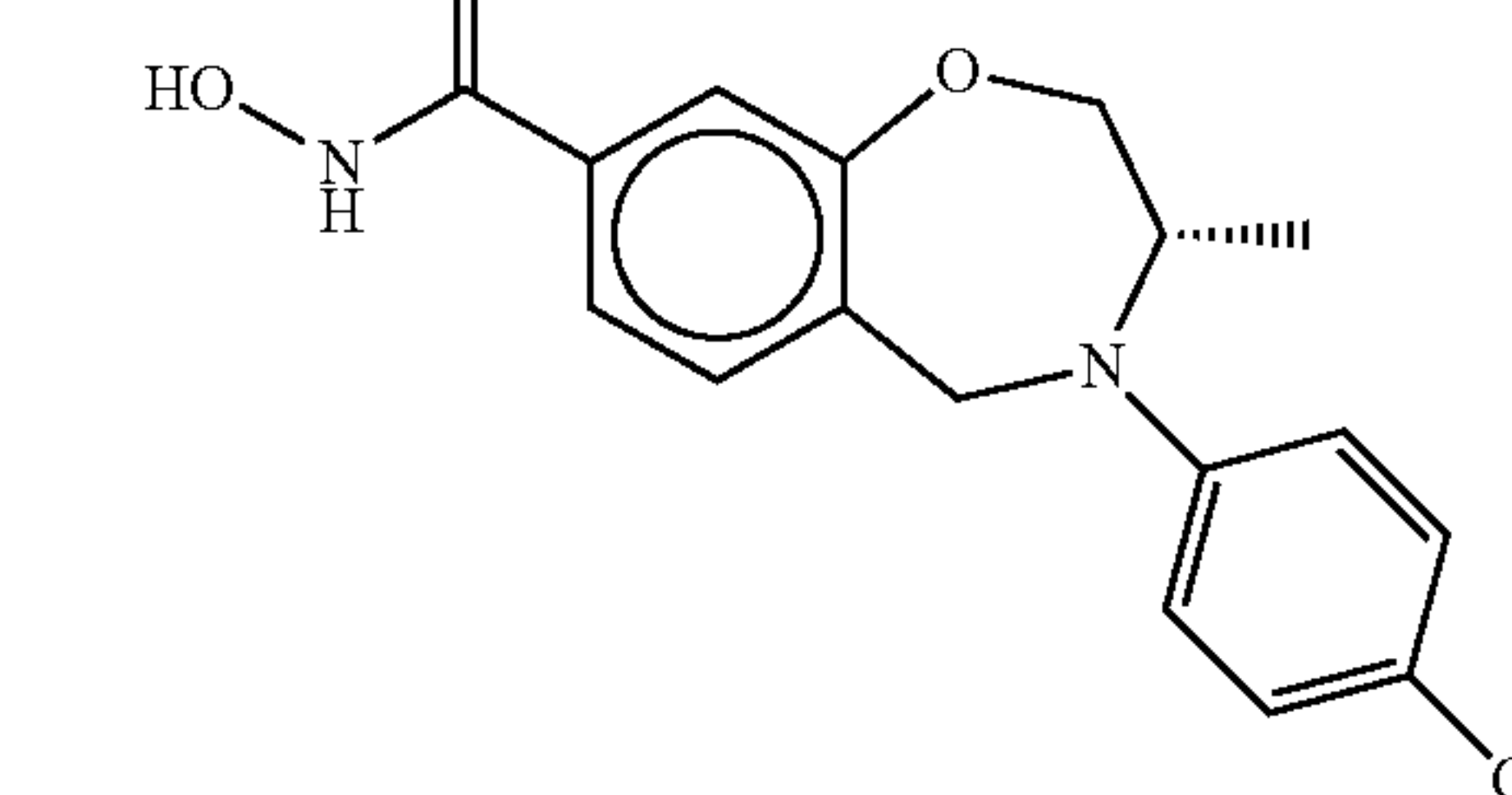
256

reaction was stirred at room temperature for 2 days, after which time the solvent was removed under vacuum. The residual solution was diluted with brine (500  $\mu$ L) and NH<sub>4</sub>OH (100  $\mu$ L), then extracted with EtOAc (2 $\times$ 500  $\mu$ L). The combined organic layers were evaporated to dryness under reduced pressure.

Step-2: (S)—N-Hydroxy-3-methyl-4-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

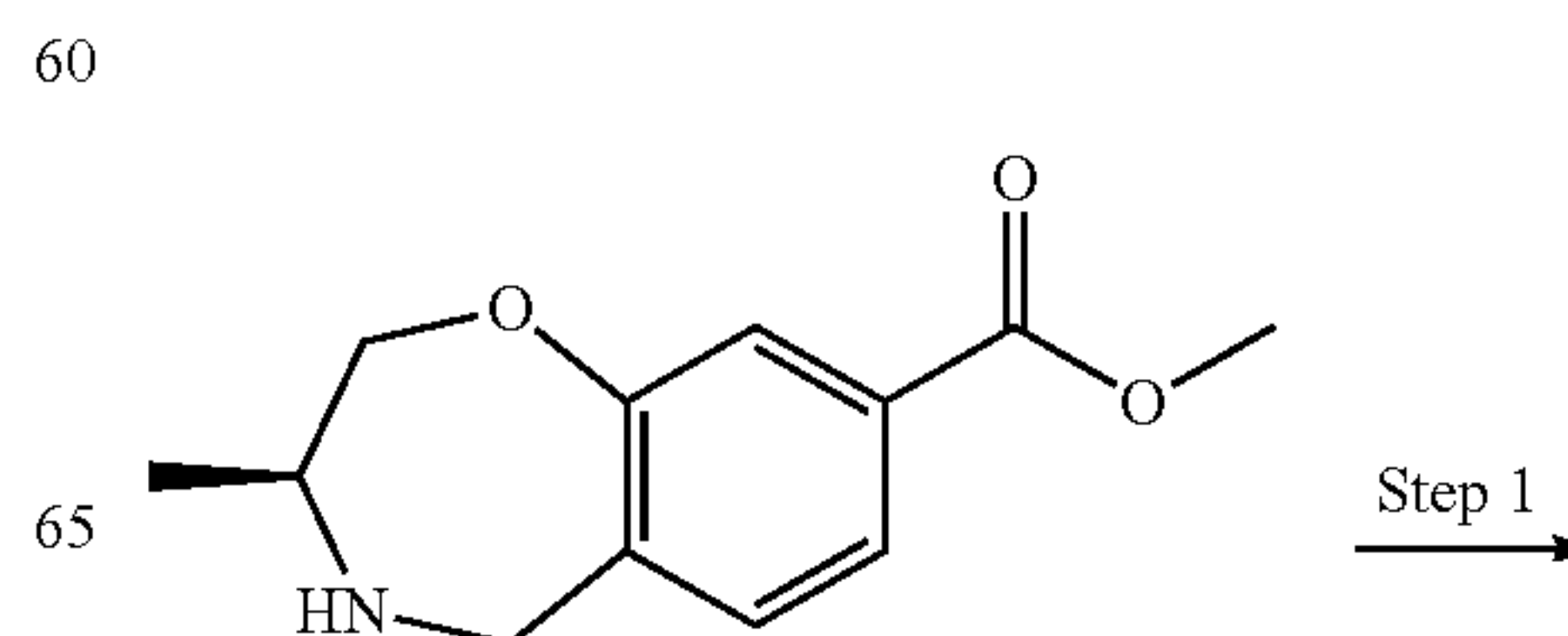
Mixed solvent of THF/MeOH (3:1, 180  $\mu$ L) was added to the vial containing methyl (S)-3-methyl-4-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate and it was shaken at 50° C. for 15 min to dissolve the residue. NH<sub>2</sub>OH (50% in water, 125  $\mu$ L) was added followed by aq. 1N NaOH (85  $\mu$ L) and the vial was sealed and shaken at room temperature overnight. The solvent was evaporated under reduce pressure and the residue was dissolved in DMSO (500  $\mu$ L) then purified by HPLC to afford the title compound (0.4 mg, 3.64% yield). MS: (ES, m/z): 367 [M+H]<sup>+</sup>.

TABLE 43

The following compounds were prepared by the parallel synthesis method of Example 87.	
Structure	Found M + H (ES)
	383
	334
	

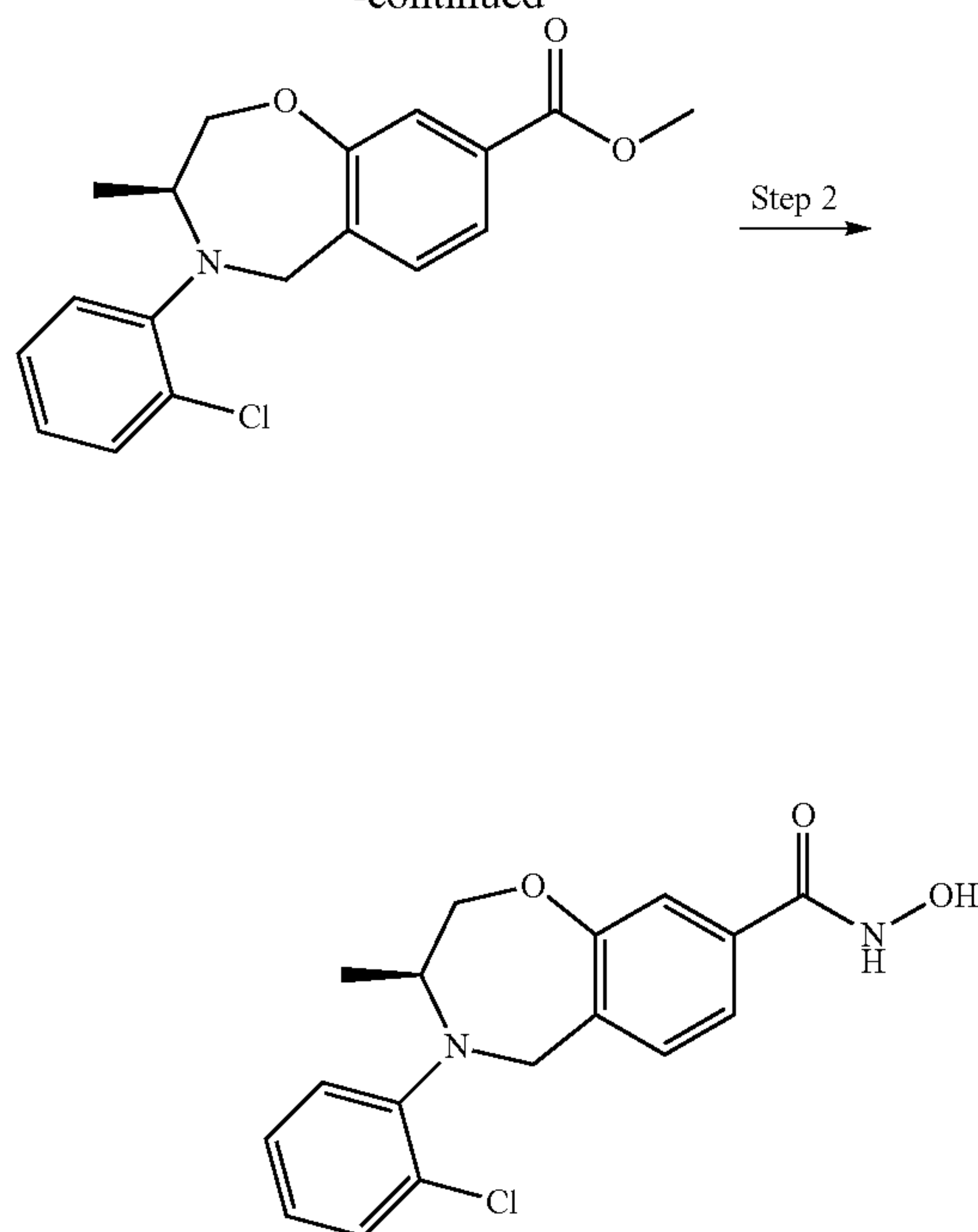
## Example 88

Preparation of (S)-4-(2-chlorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide



257

-continued



Step-1: Methyl (S)-4-(2-chlorophenyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate

Under N<sub>2</sub>, to a 2-mL reaction vial were charged methyl (S)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate (0.2M in dioxane, 150  $\mu$ L, 30  $\mu$ mol), 1-bromo-2-chlorobenzene (0.2M in toluene, 300  $\mu$ L, 60  $\mu$ mol), Xphos Pd G<sub>2</sub> (3  $\mu$ mol, 24 mg) and sodium tert-butoxide (60  $\mu$ mol, 5.7 mg), then the vial was sealed and heated at 150° C. in microwave for 90 min. The solvent was removed under vacuum. The residual solution was diluted with brine (500  $\mu$ L) and extracted with EtOAc (2 $\times$ 500  $\mu$ L). The combined organic layers were evaporated to dryness under reduced pressure.

Step-2: (S)-4-(2-Chlorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide

Mixed solvent of THF/MeOH (3:1, 180  $\mu$ L) was added to the vial containing methyl (S)-4-(2-chlorophenyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxylate and it was shaken at 50° C. for 15 min to dissolve the residue. NH<sub>2</sub>OH (50% in water, 125  $\mu$ L) was added followed by aq. 1N NaOH (85  $\mu$ L) and the vial was sealed and shaken at room temperature overnight. The solvent was evaporated under reduce pressure and the residue was dissolved in DMSO (500  $\mu$ L) then purified by HPLC to afford the title compound (0.4 mg, 4.01% yield). MS: (ES, m/z): 334 [M+H]<sup>+</sup>.

258

TABLE 44

The following compounds were prepared by the parallel synthesis method of Example 88.

Structure	Found M + H (ES)
	317

Example 89

## In Vitro Histone Deacetylase Assay

The enzymatic HDAC6 assay was performed using electrophoretic mobility shift assay. Full length human recombinant HDAC6 protein was expressed in baculoviral system and purified by affinity chromatography. The enzymatic reactions were assembled in 384 well plates in a total volume of 25  $\mu$ L in a reaction buffer composing: 100 mM HEPES, pH7.5, 25 mM KCl, 0.1% bovine serum albumin, 0.01% Triton X-100, 1% DMSO (from compounds) 2  $\mu$ M of the fluorescently labeled peptide substrate and enzyme. The enzyme was added at a final concentration of 1 nM. The peptide substrate RHKK(Ac)-NH<sub>2</sub> was used. The compounds were tested at 12 concentrations spaced by 3 $\times$  dilution intervals. Negative control samples (0%-inhibition in the absence of inhibitor) and positive control samples (100%-inhibition) were assembled in replicates of four in each assay plate. The reactions were incubated at 25° C. and quenched by the addition of 45  $\mu$ L of termination buffer (100 mM HEPES, pH 7.5, 0.01% Triton X-100, 0.05% SDS).

The terminated assay plates were analyzed on LabChip® 3000 microfluidic electrophoresis instrument (Perkin Elmer/Caliper Life Sciences). The fluorescence intensity of the electrophoretically separated de-acetylated product and substrate peptide was measured. Activity in each sample was determined as the product to sum ratio (PSR): P/(S+P), where P is the peak height of the product peptide and S is the peak height of the substrate peptide. Percent inhibition (Pinh) is determined using the following equation:

$$\text{Pinh} = (\text{PSR0\%} - \text{PSRinh}) / (\text{PSR0\%} - \text{PSR100\%}) * 100$$
 where PSRinh is the product sum ratio in the presence of inhibitor, PSR0% is the average product sum ration in the absence of inhibitor and PSR100% is the average product sum ratio in 100%-inhibition control samples. The IC<sub>50</sub> values of inhibitors were determined by fitting the %-inhibition curves with 4 parameter dose-response model using XLfit 4 software.

As set forth in Table 45, below, IC<sub>50</sub> values are defined as follows: IC<sub>50</sub>  $\leq$  0.1  $\mu$ M (+++); IC<sub>50</sub> > 0.1  $\mu$ M and  $\leq$  0.5  $\mu$ M (++); IC<sub>50</sub> > 0.5  $\mu$ M (+).



TABLE 45

Inhibitory Concentration (IC <sub>50</sub> ) Values for Representative Compounds against HDAC6.	
NAME	Activity Range
4-(1,3-benzoxazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
4-[1-(cyclohexylmethyl)-1H-1,3-benzodiazol-2-yl]-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
4-(1,3-benzothiazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
4-(cyclohexylmethyl)-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+
4-[4-cyano-3-(trifluoromethyl)phenyl]-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
4-(3,4-dichlorophenyl)-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-(pyridin-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-(pyridin-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-(pyridin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+
N-hydroxy-4-(4-methylphenyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
4-methoxyphenyl 8-(hydroxycarbamoyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-4-carboxylate	+++
cyclohexyl 8-(hydroxycarbamoyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-4-carboxylate	+++
N-hydroxy-4-(piperidine-1-sulfonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
N8-hydroxy-N4-methyl-N4-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-4,8-dicarboxamide	+
4-cyclohexyl-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+
4-[2-(dimethylamino)ethyl]-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+
N-hydroxy-4-(2-methoxyethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-[1-(oxan-4-ylmethyl)-1H-1,3-benzodiazol-2-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(2R)-N-hydroxy-2-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+
(2R)-N8-hydroxy-N4-(4-methoxyphenyl)-2-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-4,8-dicarboxamide	++
(2R)-N-hydroxy-4-(4-methoxybenzenesulfonyl)-2-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(2R)-N-hydroxy-4-[(4-methoxyphenyl)methyl]-2-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(2R)-N-hydroxy-2-methyl-4-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(2R)-N-hydroxy-2,4-dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+
(2S)-N-hydroxy-2-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(2S)-N8-hydroxy-N4-(4-methoxyphenyl)-2-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-4,8-dicarboxamide	+++
(2S)-N-hydroxy-4-(4-methoxybenzenesulfonyl)-2-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+
(2S)-N-hydroxy-2-methyl-4-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+
(2S)-N-hydroxy-2,4-dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+
(2S)-N-hydroxy-4-[(4-methoxyphenyl)methyl]-2-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-[(4-methoxyphenyl)methyl]-3,3-dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-3,3-dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
N-hydroxy-3,3,4-trimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3R)-N-hydroxy-4-[(4-methoxyphenyl)methyl]-3-(propan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++

TABLE 45-continued

Inhibitory Concentration (IC <sub>50</sub> ) Values for Representative Compounds against HDAC6.	
NAME	Activity Range
(3R)-N-hydroxy-4-phenyl-3-(propan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(3R)-N8-hydroxy-N4-(4-methoxyphenyl)-3-(propan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-4,8-dicarboxamide	++
(3R)-N-hydroxy-3-(propan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3R)-N-hydroxy-4-methyl-3-(propan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3S)-N-hydroxy-4-[(4-methoxyphenyl)methyl]-3-(propan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3S)-N-hydroxy-4-phenyl-3-(propan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3S)-N8-hydroxy-N4-(4-methoxyphenyl)-3-(propan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-4,8-dicarboxamide	+++
(3S)-N-hydroxy-3-(propan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3S)-N-hydroxy-4-methyl-3-(propan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3R)-N-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(3R)-N-hydroxy-3,4-dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3R)-N8-hydroxy-N4-(4-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-4,8-dicarboxamide	++
(3R)-N-hydroxy-4-(4-methoxybenzenesulfonyl)-3-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+
(3R)-N-hydroxy-4-[(4-methoxyphenyl)methyl]-3-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3R)-N-hydroxy-3-methyl-4-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(3S)-N8-hydroxy-N4-(4-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-4,8-dicarboxamide	+++
(3S)-N-hydroxy-4-(4-methoxybenzenesulfonyl)-3-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(3S)-N-hydroxy-4-[(4-methoxyphenyl)methyl]-3-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3S)-N-hydroxy-3-methyl-4-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
(3S)-N-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(3S)-N-hydroxy-3,4-dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
(5R/5S)-N-hydroxy-4-[(4-methoxyphenyl)methyl]-5-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide,	+
(5S/5R)-N-hydroxy-4-[(4-methoxyphenyl)methyl]-5-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide,	+
N8-hydroxy-N4-(4-methoxyphenyl)-2H,3H,4H,5H-pyrido[2,3-f][1,4]oxazepine-4,8-dicarboxamide	+++
N-hydroxy-4-(4-methoxybenzenesulfonyl)-2H,3H,4H,5H-pyrido[2,3-f][1,4]oxazepine-8-carboxamide	++
N-hydroxy-4-[(4-methoxyphenyl)methyl]-2H,3H,4H,5H-pyrido[2,3-f][1,4]oxazepine-8-carboxamide	++
N8-hydroxy-N4-(4-methoxyphenyl)-2H,3H,4H,5H-pyrido[3,2-f][1,4]oxazepine-4,8-dicarboxamide	+
N-hydroxy-4-(4-methoxybenzenesulfonyl)-2H,3H,4H,5H-pyrido[3,2-f][1,4]oxazepine-8-carboxamide	+
N-hydroxy-4-[(4-methoxyphenyl)methyl]-2H,3H,4H,5H-pyrido[3,2-f][1,4]oxazepine-8-carboxamide	+
N-hydroxy-4-[(4-methoxyphenyl)methyl]-5-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-[2-(4-methoxyphenyl)ethyl]-5-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-[(4-methoxyphenyl)methyl]-5-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	+
N-hydroxy-4-[2-(4-methoxyphenyl)ethyl]-5-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	++
N-hydroxy-4-[2-(4-methoxyphenyl)ethyl]-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-8-carboxamide	+
4-(1H-1,3-benzodiazol-2-ylmethyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-8-carboxamide	++
4-(1H-1,3-benzodiazol-2-ylmethyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
N-hydroxy-4-[2-(4-methoxyphenyl)ethyl]-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++



TABLE 45-continued

Inhibitory Concentration (IC <sub>50</sub> ) Values for Representative Compounds against HDAC6.	
NAME	Activity Range
N-hydroxy-2-oxo-4-(1-phenylethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
N-hydroxy-4-[(4-methoxyphenyl)methyl]-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-4-(4-methoxybenzenesulfonyl)-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
N-hydroxy-2-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
N-hydroxy-4-[(4-methoxyphenyl)methyl]-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
N-hydroxy-4-[(4-methoxyphenyl)methyl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
N-hydroxy-4-[(4-methoxyphenyl)methyl]-1-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
2-benzyl-N-hydroxy-1,1-dioxo-3,4-dihydro-2H-5,1λ <sup>6</sup> ,2-benzoxathiazepine-8-carboxamide	++
2-benzyl-N-hydroxy-1,1-dioxo-3,4-dihydro-2H-5,1λ <sup>6</sup> ,2-benzoxathiazepine-7-carboxamide	+
N8-hydroxy-N4-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-4,8-dicarboxamide	++
N7-hydroxy-N4-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-4,7-dicarboxamide	+
N-hydroxy-4-(4-methoxybenzenesulfonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-(4-methoxybenzenesulfonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	++
4-(1H-1,3-benzodiazol-2-ylmethyl)-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
4-(1H-1,3-benzodiazol-2-ylmethyl)-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	+
N-hydroxy-4-{[1-(2-methoxyethyl)-1H-1,3-benzodiazol-2-yl]methyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-{[1-(2-methoxyethyl)-1H-1,3-benzodiazol-2-yl]methyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	+
N-hydroxy-4-[2-(4-methoxyphenyl)ethyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-[2-(4-methoxyphenyl)ethyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	+
N-hydroxy-4-[(4-methoxyphenyl)methyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-[(4-methoxyphenyl)methyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	+
4-(1H-1,3-benzodiazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
4-(1H-1,3-benzodiazol-2-yl)-N-hydroxy-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	++
N-hydroxy-4-[1-(2-methoxyethyl)-1H-1,3-benzodiazol-2-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	+++
N-hydroxy-4-[1-(2-methoxyethyl)-1H-1,3-benzodiazol-2-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-{[5-(propan-2-yl)pyridin-2-yl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-(pyridin-4-ylmethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-(pyridin-2-ylmethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
N-hydroxy-2-oxo-4-(1,3-thiazol-2-ylmethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
N-hydroxy-2-oxo-4-{[4-(propan-2-yloxy)phenyl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
N-hydroxy-2-oxo-4-{[4-(trifluoromethoxy)phenyl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-[(3-phenoxyphenyl)methyl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-[(4-phenoxyphenyl)methyl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
N-hydroxy-2-oxo-4-{[3-(trifluoromethoxy)phenyl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-{[2-(trifluoromethoxy)phenyl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
N-hydroxy-2-oxo-4-{[4-(pyridin-2-yl)phenyl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
N-hydroxy-2-oxo-4-{[4-(1H-pyrazol-1-yl)phenyl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++

TABLE 45-continued

Inhibitory Concentration (IC <sub>50</sub> ) Values for Representative Compounds against HDAC6.	
NAME	Activity Range
4-[(4-cyanophenyl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-(pyrimidin-5-ylmethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
N-hydroxy-4-(naphthalen-1-ylmethyl)-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
4-{[2-(3-fluorophenyl)-1,3-oxazol-4-yl]methyl}-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
4-({3-[(dimethylamino)methyl]phenyl)methyl}-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
4-benzyl-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-{[4-(propan-2-yl)phenyl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
4-[(4-chlorophenyl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
4-[(2,5-difluorophenyl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
4-[(3,5-difluorophenyl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
4-[(3,5-dichlorophenyl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
4-[(2-fluoro-4-methoxyphenyl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
4-[(2-chlorophenyl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
4-[(2,2-difluoro-2H-1,3-benzodioxol-4-yl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
N-hydroxy-2-oxo-4-(pyridin-3-ylmethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-4-[(1-methyl-1H-imidazol-2-yl)methyl]-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
4-[(1-acetylpiperidin-3-yl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
N-hydroxy-4-{imidazo[1,2-a]pyridin-2-ylmethyl}-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
4-(cyclopropylmethyl)-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-(oxolan-3-ylmethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
4-[(dimethyl-1,3-thiazol-2-yl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
4-[(3-chlorophenyl)methyl]-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
4-{[4-(tert-butoxy)phenyl]methyl}-N-hydroxy-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-{[1-(propan-2-yl)piperidin-4-yl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+
N-hydroxy-2-oxo-4-{[4-(1H-pyrrol-1-yl)phenyl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
N-hydroxy-4-(naphthalen-2-ylmethyl)-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
N-hydroxy-4-{[2-(morpholin-4-yl)pyridin-4-yl]methyl}-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-4-{imidazo[1,2-a]pyridin-7-ylmethyl}-2-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	++
N-hydroxy-2-oxo-4-{[4-(1,3-thiazol-2-yl)phenyl]methyl}-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-7-carboxamide	+++
N-hydroxy-4-[(6-methoxypyridin-3-yl)methyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-[(6-methoxypyridin-3-yl)methyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	+
N-hydroxy-4-[(5-methoxypyridin-2-yl)methyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-8-carboxamide	++
N-hydroxy-4-[(5-methoxypyridin-2-yl)methyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-carboxamide	+
(R)-N8-hydroxy-2-isopropyl-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+
(R)-N8-hydroxy-2-(methoxymethyl)-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	++
(S)-N8-hydroxy-2-(methoxymethyl)-N4-(4-methoxyphenyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	++
(R)-N8-hydroxy-N4-(4-methoxyphenyl)-2-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	++



TABLE 45-continued

Inhibitory Concentration (IC <sub>50</sub> ) Values for Representative Compounds against HDAC6.	
NAME	Activity Range
(S)-N8-hydroxy-N4-(4-methoxyphenyl)-2-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
N-hydroxy-4-methyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxamide	+++
N-hydroxy-4-phenyl-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxamide	++
N-hydroxy-4-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[benzo[f][1,4]oxazepine-3,1'-cyclopropane]-8-carboxamide	+++
(S)-3-ethyl-N-hydroxy-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-3-ethyl-N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-3-ethyl-N-hydroxy-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-3-ethyl-N-hydroxy-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-isopropyl-4-(pyridin-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-isopropyl-4-(pyridin-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-isopropyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+
(S)-N-hydroxy-3-methyl-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-4-(2-methoxyphenyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-methyl-4-(pyridin-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-methyl-4-(pyrrolidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-methyl-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-4-(isoindoline-2-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-4-(4-methoxypiperidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-methyl-4-(4-methylpiperazine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(3S)-N-hydroxy-3-methyl-4-(2-methylpiperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(3S)-N-hydroxy-3-methyl-4-(3-methylmorpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-methyl-4-(oxetan-3-ylmethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(4-fluorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(3-fluorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-methyl-4-(4-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
methyl (S)-8-(hydroxycarbarnoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate	+++
isopropyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate	+++
(S)-N-hydroxy-3-methyl-4-(methylsulfonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(ethylsulfonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N8-hydroxy-N4,N4,3-trimethyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
(S)-N-hydroxy-4-((2-methoxyethyl)sulfonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(S)-N8-hydroxy-N4-(2-methoxyethyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
(S)-N8-hydroxy-3-methyl-N4-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
(S)-N-hydroxy-3-methyl-4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(3S)-N8-hydroxy-N4-(2-methoxyethyl)-N4,3-dimethyl-2,3,7,8-tetrahydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
(S)-N-hydroxy-3-methyl-4-(pyridin-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-methyl-4-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++

TABLE 45-continued

Inhibitory Concentration (IC <sub>50</sub> ) Values for Representative Compounds against HDAC6.	
NAME	Activity Range
(S)-N-hydroxy-4-(3-methoxypropyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(3S)-4-(1-(4-fluorophenyl)ethyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(S)-N-hydroxy-3-methyl-4-(3-morpholinopropyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(3S)-N-hydroxy-3-methyl-4-(2-(tetrahydrofuran-2-yl)ethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-ethyl-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(S)-N-hydroxy-4-isopropyl-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxarmide	+
(S)-N-hydroxy-4-isobutyl-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(cyclobutylmethyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(cyclopropylmethyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(4-fluorobenzyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(cyclohexylmethyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-methyl-4-(2-morpholinoethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(S)-N-hydroxy-4-(2-methoxyethyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(cyclopentylmethyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(3S)-N-hydroxy-3-methyl-4-((tetrahydrofuran-2-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-cyclopentyl-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(S)-4-((4-fluorophenyl)sulfonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
cyclopentyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate	+++
cyclohexyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate	+++
(S)-N8-hydroxy-N4,3-dimethyl-N4-phenyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	++
ethyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate	+++
cyclobutyl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate	+++
tetrahydro-2H-pyran-4-yl (S)-8-(hydroxycarbamoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate	+++
4-fluorophenyl (S)-8-(hydroxycarbarnoyl)-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate	+++
(S)-N-hydroxy-3-methyl-4-(oxetan-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+
(R)-N-hydroxy-3-(methoxymethyl)-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(R)-N-hydroxy-4-(4-methoxybenzyl)-3-(methoxymethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(R)-N-hydroxy-3-(methoxymethyl)-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(R)-N-hydroxy-3-(methoxymethyl)-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-(methoxymethyl)-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-4-(4-methoxybenzyl)-3-(methoxymethyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-(methoxymethyl)-4-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-3-(methoxymethyl)-4-(o-tolyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
N-hydroxy-4-(pyrrolidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
N-hydroxy-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
N-hydroxy-4-(4-methylpiperazine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+
N-hydroxy-4-(4-methoxypiperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++



TABLE 45-continued

Inhibitory Concentration (IC <sub>50</sub> ) Values for Representative Compounds against HDAC6.	
NAME	Activity Range
N-hydroxy-4-(isoindoline-2-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
N-hydroxy-4-(2-methylpiperidine-1-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
N-hydroxy-4-(3-methylmorpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(R)-N-hydroxy-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+
(S)-N-hydroxy-4-(4-methoxybenzyl)-5-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(S)-N-hydroxy-3-methyl-4-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(S)-N-hydroxy-3-methyl-4-(4-(trifluoromethoxy)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	++
(S)-4-(4-chlorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(2-chlorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(2-fluorophenyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(azetidine-1-carbonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N-hydroxy-4-(3-methoxyazetidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(3S)-N-hydroxy-4-(3-methoxypyrrolidine-1-carbonyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-N8-hydroxy-3-methyl-N4-(pyridin-3-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
(S)-N4-cyclohexyl-N8-hydroxy-3-methyl-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
(S)-N8-hydroxy-3-methyl-N4-(pyridin-2-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
(S)-N8-hydroxy-3-methyl-N4-(tetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
(S)-N8-hydroxy-N4,3-dimethyl-N4-(tetrahydro-2H-pyran-4-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
(S)-N8-hydroxy-3-methyl-N4-(pyridin-4-yl)-2,3-dihydrobenzo[f][1,4]oxazepine-4,8(5H)-dicarboxamide	+++
(S)-4-((1R,5R)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-((1S,5S)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
(S)-4-(3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-N-hydroxy-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++
N-hydroxy-2-oxo-4-(piperidine-1-carbonyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-7-carboxamide	++
(S)-3-benzyl-N-hydroxy-4-(morpholine-4-carbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-8-carboxamide	+++

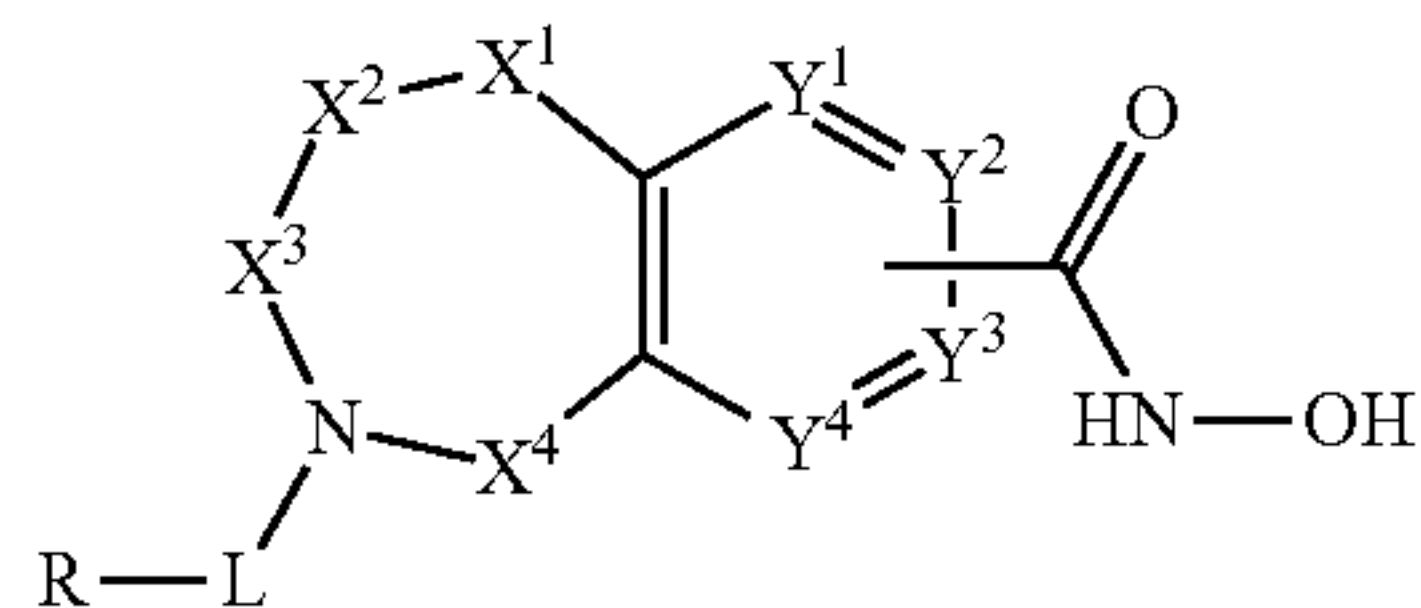
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## EQUIVALENTS

While the present disclosure has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present disclosure.

The invention claimed is:

1. A compound of Formula I:



or a pharmaceutically acceptable salt, thereof, wherein:

X<sup>1</sup> is O;

X<sup>2</sup> and X<sup>4</sup> are each CR<sup>1</sup>R<sup>2</sup>;

X<sup>3</sup> is CR<sup>1</sup>R<sup>2</sup>;

Y<sup>1</sup> and Y<sup>4</sup> are not bonded to —C(O)NHOH and are each independently N or CR<sup>1</sup>;

Y<sup>2</sup> and Y<sup>3</sup> are each independently N or CR<sup>1</sup> when not bonded to —C(O)NHOH and Y<sup>2</sup> and Y<sup>3</sup> are C when bonded to —C(O)NHOH;

wherein one of Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup>, and Y<sup>4</sup> is N;

L is selected from a group consisting of a bond, —(CR<sup>1</sup>R<sup>2</sup>)<sub>n</sub>—, —C(O)O—, —C(O)NR<sup>3</sup>—, —S(O)<sub>2</sub>—, —S(O)<sub>2</sub>NR<sup>3</sup>—, —S(O)—, and —S(O)NR<sup>3</sup>—, wherein L is bound to the ring nitrogen through the carbonyl or sulfonyl group;

R is independently selected from the group consisting of —H, —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>2</sub>-C<sub>6</sub> alkenyl, —C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, —C<sub>2</sub>-C<sub>6</sub> alkynyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, —C<sub>5</sub>-C<sub>12</sub> spirocyclyl, heterocyclyl, spiroheterocyclyl, aryl, and heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, spirocyclyl, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from the group consisting of —OH, halogen, oxo, —NO<sub>2</sub>, —CN, —R<sup>1</sup>, —R<sup>2</sup>, —OR<sup>3</sup>, —NHR<sup>3</sup>, —NR<sup>3</sup>R<sup>4</sup>, —S(O)<sub>2</sub>NR<sup>3</sup>R<sup>4</sup>, —S(O)<sub>2</sub>R<sup>1</sup>, —C(O)R<sup>1</sup>, —CO<sub>2</sub>R<sup>1</sup>, —NR<sup>3</sup>S(O)<sub>2</sub>R<sup>1</sup>, —S(O)R<sup>1</sup>, —S(O)NR<sup>3</sup>R<sup>4</sup>, —NR<sup>3</sup>S(O)R<sup>1</sup>, heterocyclyl, aryl, and heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O;

each R<sup>1</sup> and R<sup>2</sup> are independently, and at each occurrence, selected from the group consisting of —H, —R<sup>3</sup>, —R<sup>4</sup>, —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>2</sub>-C<sub>6</sub> alkenyl, —C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, —C<sub>2</sub>-C<sub>6</sub> alkynyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, —OH, halogen, —NO<sub>2</sub>, —CN, —NHC<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>R<sup>5</sup>, —S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), —(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>R<sup>5</sup>, —C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, —CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, and —(CHR<sup>5</sup>)<sub>n</sub>NR<sup>3</sup>R<sup>4</sup>, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from the group consisting of —OH, halogen, —NO<sub>2</sub>, oxo, —CN, —R<sup>5</sup>, —OR<sup>3</sup>,

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—NHR<sup>3</sup>, —NR<sup>3</sup>R<sup>4</sup>, —S(O)<sub>2</sub>N(R<sup>3</sup>)<sub>2</sub>, —S(O)<sub>2</sub>R<sup>5</sup>, —C(O)R<sup>5</sup>, —CO<sub>2</sub>R<sup>5</sup>, —NR<sup>3</sup>S(O)<sub>2</sub>R<sup>5</sup>, —S(O)R<sup>5</sup>, —S(O)NR<sup>3</sup>R<sup>4</sup>, —NR<sup>3</sup>S(O)R<sup>5</sup>, heterocyclyl, aryl, and heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O;

R<sup>1</sup> and R<sup>2</sup> are independently, and at each occurrence, selected from the group consisting of —H, —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>2</sub>-C<sub>6</sub> alkenyl, —C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, —C<sub>2</sub>-C<sub>6</sub> alkynyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocyclyl, —OH, halogen, —NO<sub>2</sub>, —CN, —NHC<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>R<sup>5</sup>, —S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), —(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>R<sup>5</sup>, —C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, —CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, and —(CHR<sup>5</sup>)<sub>n</sub>NR<sup>3</sup>R<sup>4</sup>, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, or heterocyclyl is optionally substituted with one or more substituents selected from the group consisting of —OH, halogen, —NO<sub>2</sub>, oxo, —CN, —R<sup>5</sup>, —OR<sup>3</sup>, —NHR<sup>3</sup>, —NR<sup>3</sup>R<sup>4</sup>, —S(O)<sub>2</sub>N(R<sup>3</sup>)<sub>2</sub>, —S(O)<sub>2</sub>R<sup>5</sup>, —C(O)R<sup>5</sup>, —CO<sub>2</sub>R<sup>5</sup>, —NR<sup>3</sup>S(O)<sub>2</sub>R<sup>5</sup>, —S(O)R<sup>5</sup>, —S(O)NR<sup>3</sup>R<sup>4</sup>, —NR<sup>3</sup>S(O)R<sup>5</sup>, heterocyclyl, aryl, and heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O;

R<sup>3</sup> and R<sup>4</sup> are independently, at each occurrence, selected from the group consisting of —H, —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>2</sub>-C<sub>6</sub> alkenyl, —C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, —C<sub>2</sub>-C<sub>6</sub> alkynyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, —S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), —(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>R<sup>5</sup>, —C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, —CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, or —(CHR<sup>5</sup>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from the group consisting of —OH, halogen, —NO<sub>2</sub>, oxo, —CN, —R<sup>5</sup>, —O(C<sub>1</sub>-C<sub>6</sub> alkyl), —NH(C<sub>1</sub>-C<sub>6</sub> alkyl), —N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), —C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, —CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —S(O)R<sup>5</sup>, —S(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)R<sup>5</sup>, heterocyclyl, aryl, and heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O;

or R<sup>3</sup> and R can combine with the nitrogen atom to which they are attached to form a heterocycle, wherein each heterocycle is optionally substituted by —R<sup>1</sup>, —R<sup>2</sup>, —R<sup>4</sup>, —OR<sup>4</sup>, or —NR<sup>4</sup>R<sup>5</sup>;

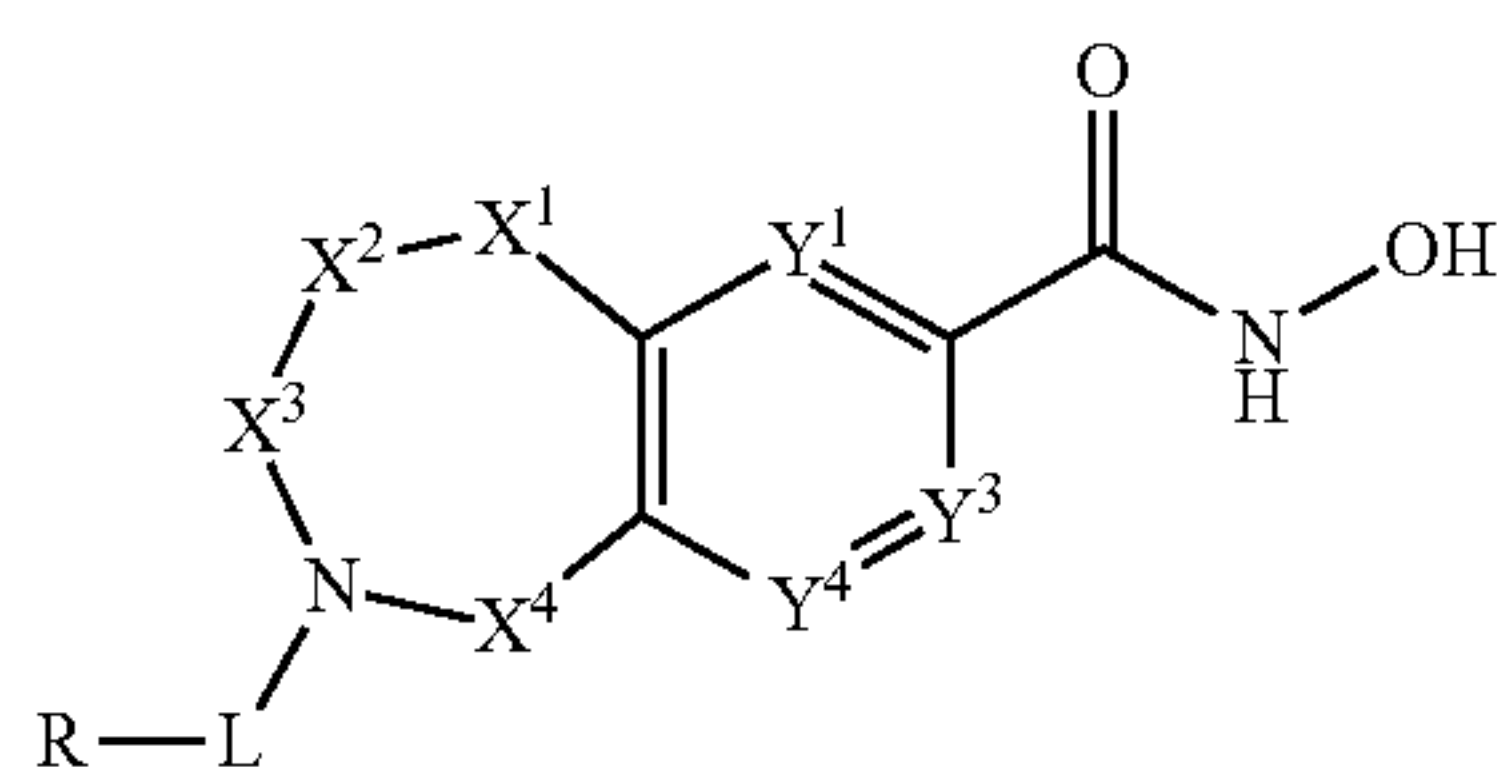
R<sup>5</sup> is independently, and at each occurrence, selected from the group consisting of —H, —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>2</sub>-C<sub>6</sub> alkenyl, —C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, —C<sub>2</sub>-C<sub>6</sub> alkynyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, —OH, halogen, —NO<sub>2</sub>, —CN, —NHC<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), —S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —S(O)<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —C(O)C<sub>1</sub>-C<sub>6</sub> alkyl, —CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)SO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, —S(O)(C<sub>1</sub>-C<sub>6</sub> alkyl), —S(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, —N(C<sub>1</sub>-C<sub>6</sub> alkyl)S(O)(C<sub>1</sub>-C<sub>6</sub> alkyl), and —(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>; and

n is independently, and at each occurrence, an integer from 0 to 6.



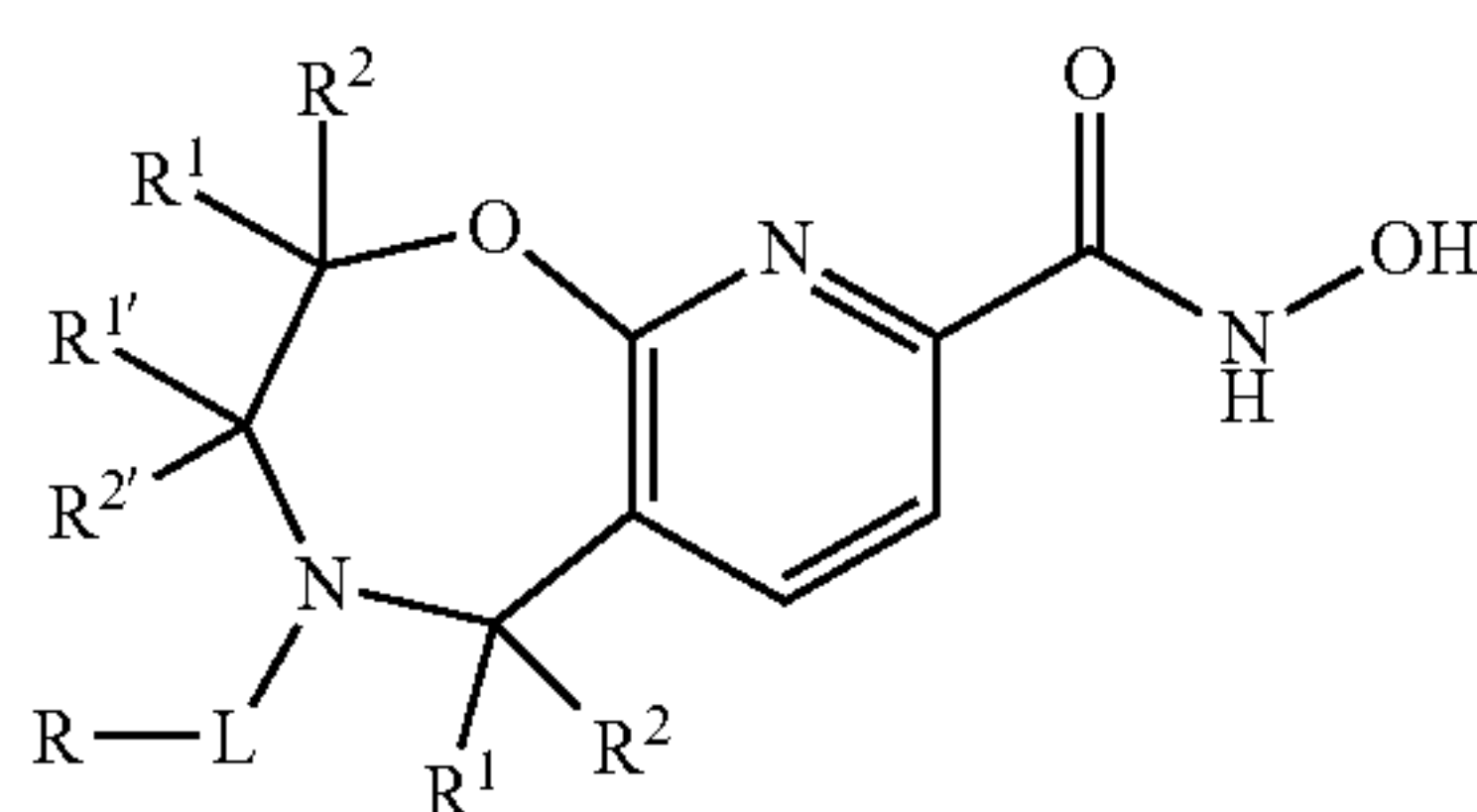
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2. The compound of claim 1, wherein the compound is of the Formula IA:



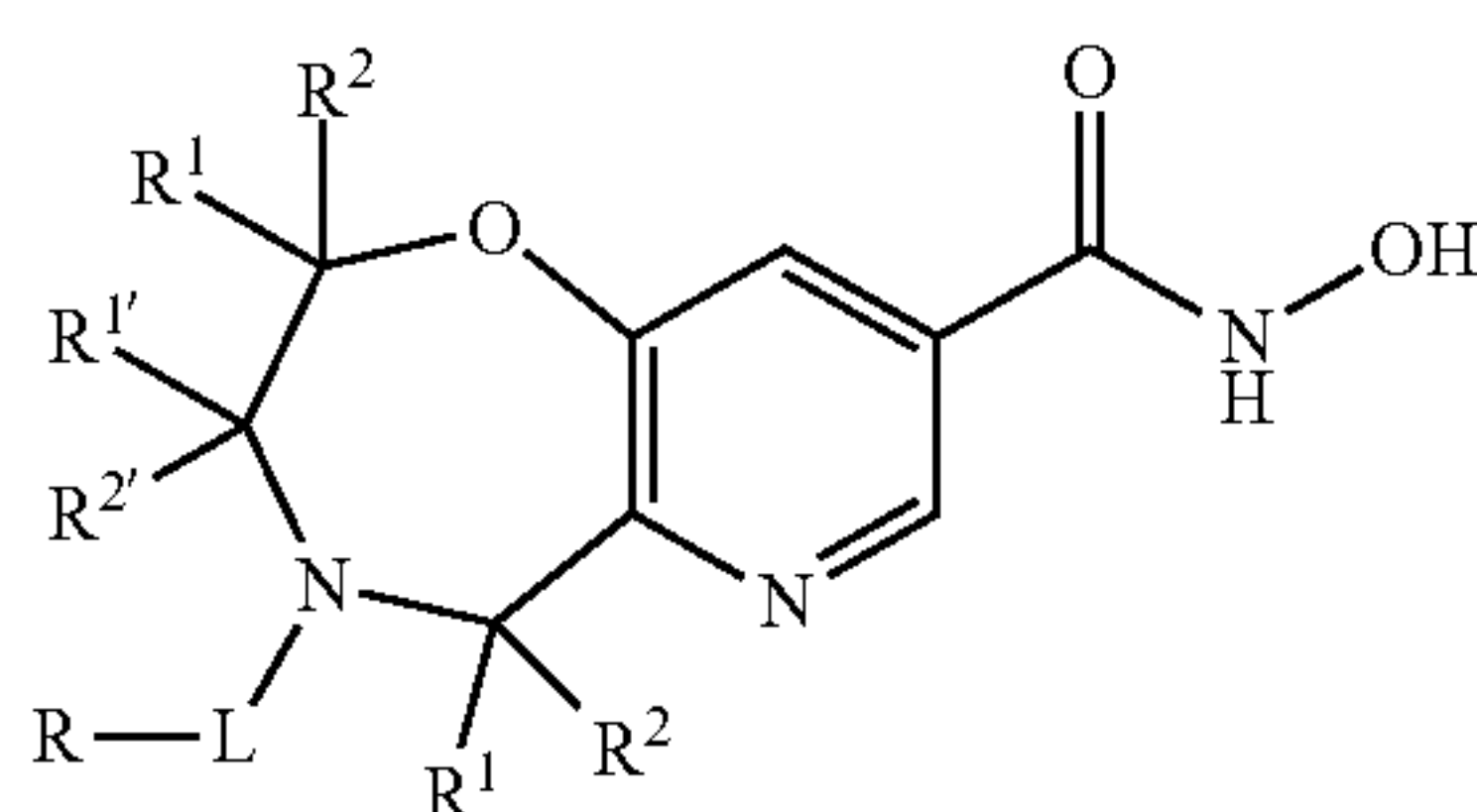
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2, wherein the compound is of the Formula IA-2:



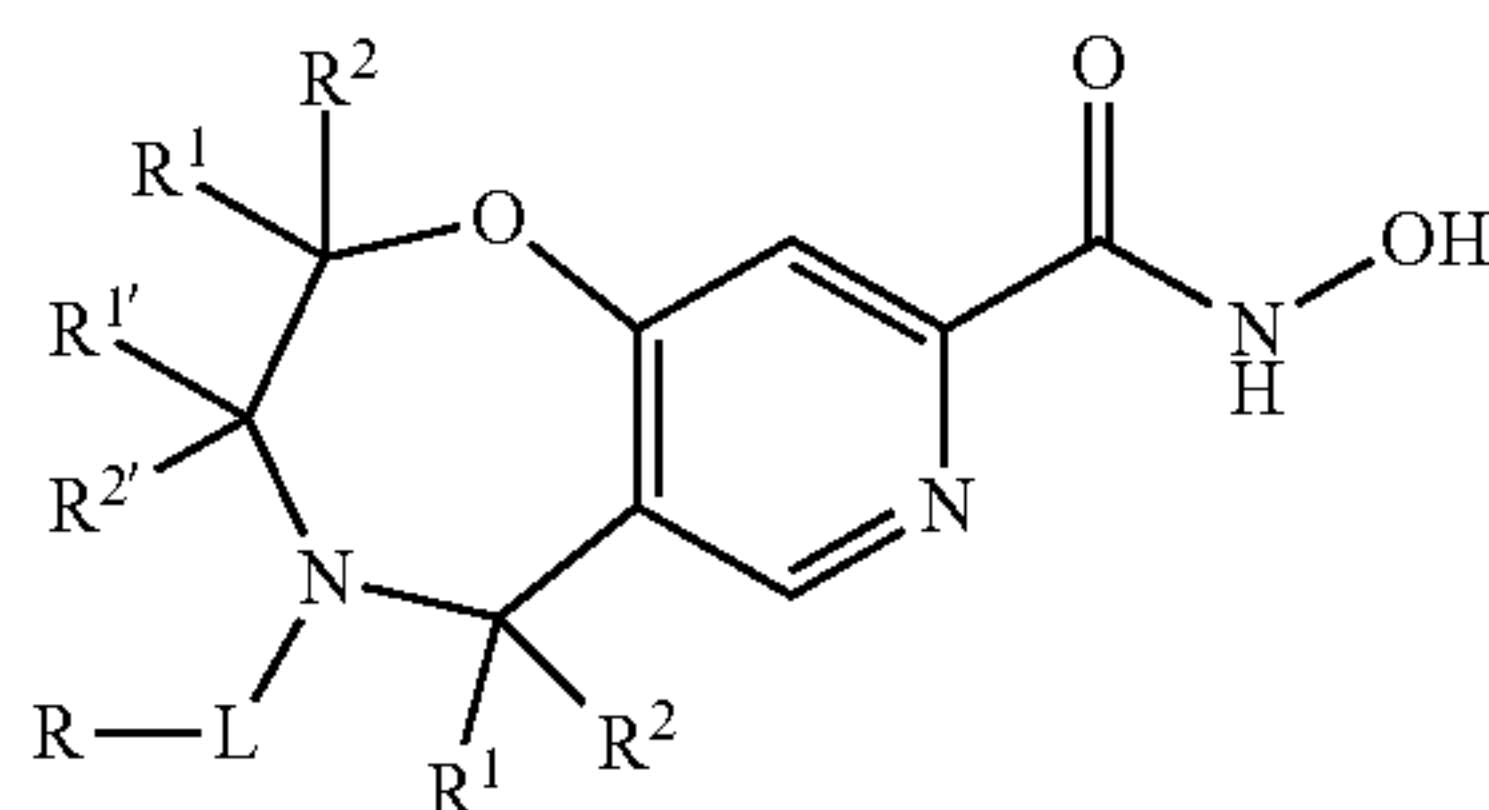
or a pharmaceutically acceptable salt thereof.

4. The compound of claim 2, wherein the compound is of the Formula IA-3:



or a pharmaceutically acceptable salt thereof.

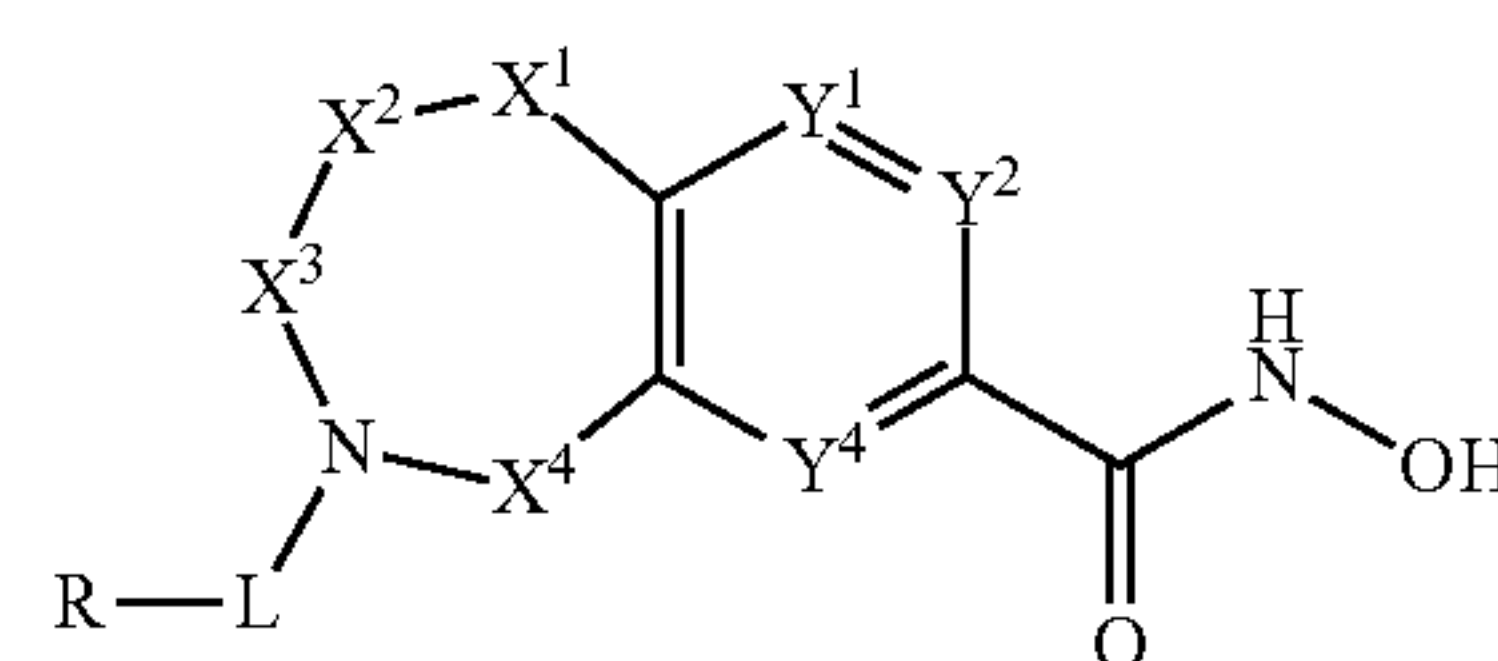
5. The compound of claim 2, wherein the compound is of the Formula IA-4:



or a pharmaceutically acceptable salt thereof.

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6. The compound of claim 1, wherein the compound is of the Formula IB



or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1 selected from the group consisting of:

- N8-hydroxy-N4-(4-methoxyphenyl)-2,3-dihydropyrido [2,3-f][1,4]oxazepine-4,8(5H)-dicarboxamide;
- N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxamide;
- N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine-8-carboxamide;
- N8-hydroxy-N4-(4-methoxyphenyl)-2,3-dihydropyrido [3,2-f][1,4]oxazepine-4,8(5H)-dicarboxamide;
- N-hydroxy-4-((4-methoxyphenyl)sulfonyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxamide; and
- N-hydroxy-4-(4-methoxybenzyl)-2,3,4,5-tetrahydropyrido[3,2-f][1,4]oxazepine-8-carboxamide.

8. The compound of claim 1, wherein at least one of R<sup>1'</sup> and R<sup>2'</sup> is —H.

9. The compound of claim 8, wherein one of R<sup>1'</sup> and R<sup>2'</sup> is —C<sub>1</sub>-C<sub>6</sub> alkyl.

10. The compound of claim 9, wherein L is —C(O)NR<sup>3</sup>—.

11. The compound of claim 10, wherein R<sup>3</sup> and R combine with the nitrogen atom to which they are attached to form an optionally substituted heterocycle.

12. The compound of claim 8, wherein L is —(CR<sup>1</sup>R<sup>2</sup>)<sub>n</sub>—, —C(O)O—, —C(O)NR<sup>3</sup>—, or —S(O)<sub>2</sub>—.

13. The compound of claim 12, wherein R is an optionally substituted group selected from the group consisting of —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocyclyl, aryl, and heteroaryl.

14. The compound of claim 8, wherein R<sup>1'</sup> and R<sup>2'</sup> are each —H.

15. The compound of claim 14, wherein L is —C(O)NR<sup>3</sup>—, —S(O)<sub>2</sub>—, or —(CR<sup>1</sup>R<sup>2</sup>)<sub>n</sub>—.

16. The compound of claim 15, wherein R is optionally substituted aryl.

17. The compound of claim 9, wherein L is a bond.

18. The compound of claim 17, wherein R is an optionally substituted group selected from the group consisting of —C<sub>1</sub>-C<sub>6</sub> alkyl, —C<sub>3</sub>-C<sub>8</sub> cycloalkyl, heterocyclyl, aryl, and heteroaryl.

19. The compound of claim 18, wherein R is —C<sub>1</sub>-C<sub>6</sub> alkyl substituted with an optionally substituted group selected from the group consisting of aryl, heteroaryl, and —C<sub>3</sub>-C<sub>8</sub> cycloalkyl.

20. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier.

\* \* \* \* \*